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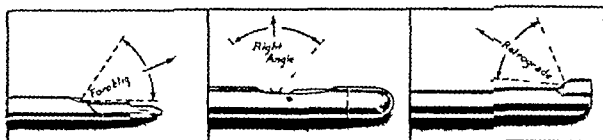
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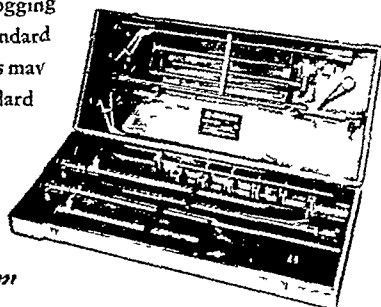
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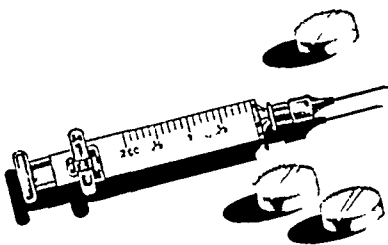
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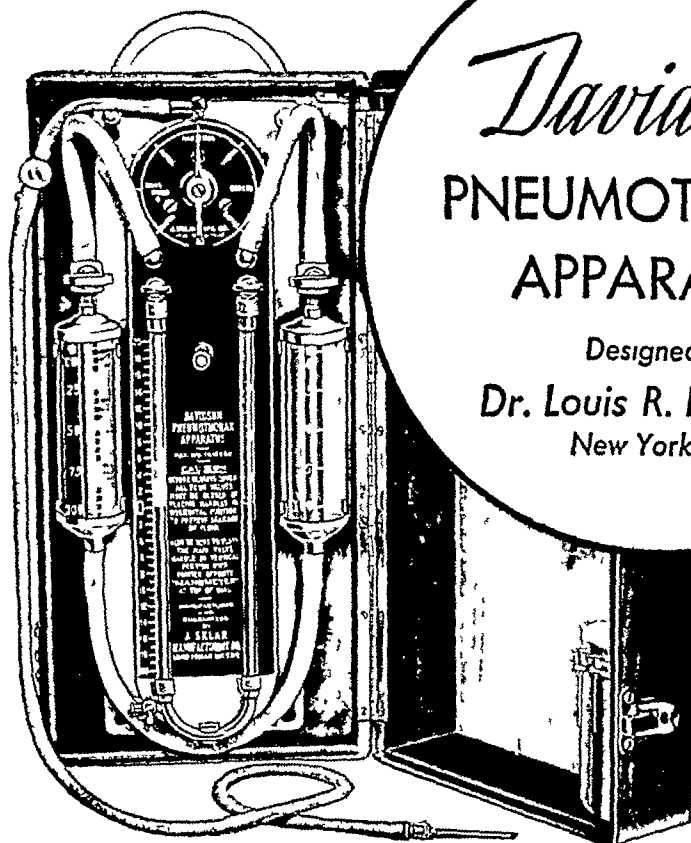
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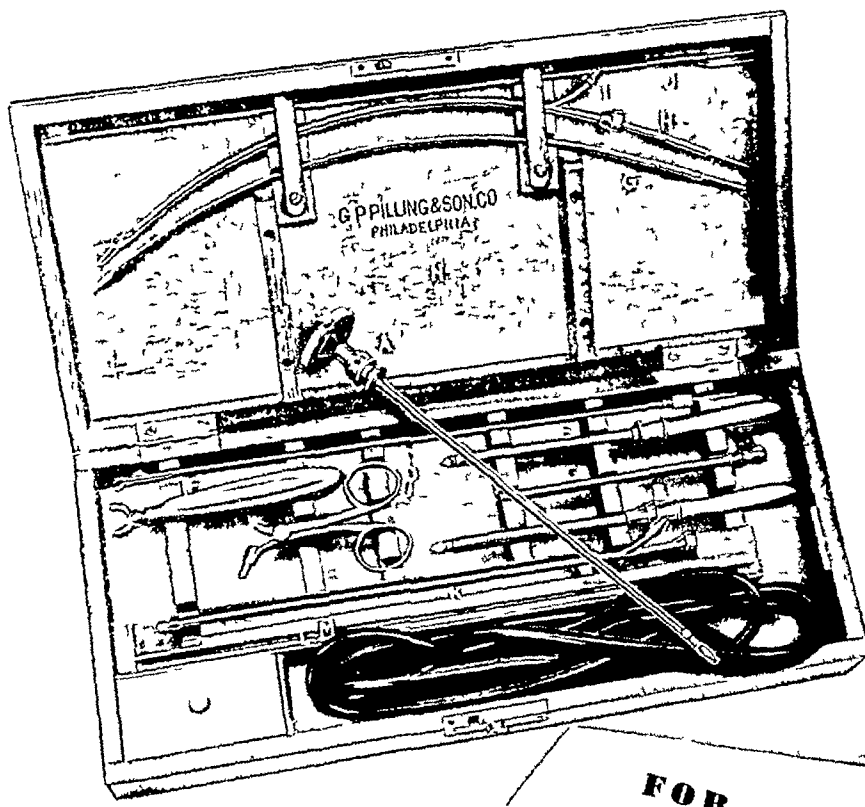
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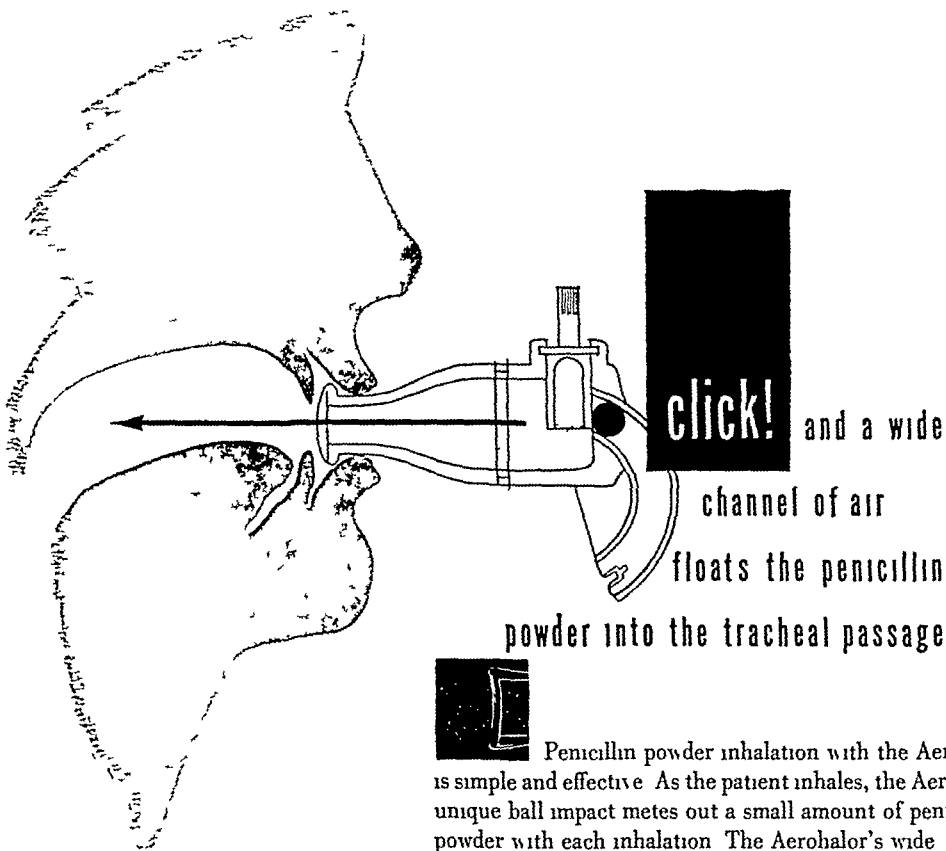


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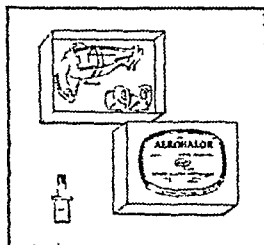
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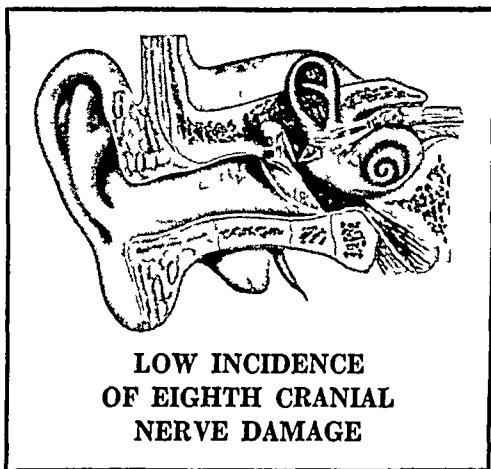
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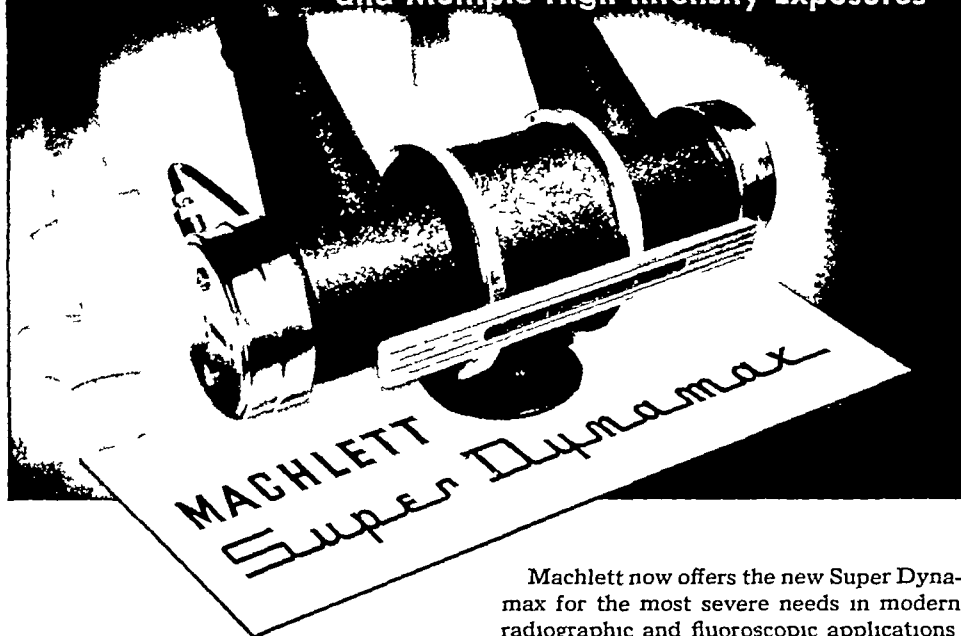


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DISEASES *of the* CHEST

VOLUME XVI

JULY 1949

NUMBER 1

Use of Para-Aminosalicylic Acid in Chronic Pulmonary Tuberculosis*

CHESMORE EASTLAKE, JR., MD and

ALVAN L. BARACH, MD, F C C P

New York, New York

Introduction

In 1940, Bernheim¹ made the interesting observation that the oxygen consumption of tubercle bacilli was increased by salicylic and benzoic acid. Lehmann^{2,3} studied various derivatives of benzoic acid with the purpose of discovering a substance possessing bacterio-static properties against the tubercle bacillus and found that para-aminosalicylic acid (PAS) was the most effective. Demonstration that the drug produced an inhibitory effect in vitro was confirmed by Sievers⁴ and by Youmans,⁵ and a retarding effect on the development of experimental tuberculosis was shown for mice by Youmans⁵ and for guinea pigs by Feldman, Karlson and Hinshaw.⁶ Trial of the drug by Lehmann and his collaborators^{2,3,7,8} in chronic pulmonary tuberculosis indicated that a favorable clinical effect was produced on the symptoms of the disease, especially cough, expectoration and fever. No serious toxic effects of administration of para-aminosalicylic acid were reported by the Swedish investigators who have used the drug for three years. The side effects consisted of nausea, vomiting and transient albuminuria.

The effectiveness of PAS was studied in vitro and animal experiments, as well as its clinical use in a small series of cases of chronic pulmonary tuberculosis.

The purpose of Part I of this paper is to describe the inhibitory

*From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York. We wish to acknowledge the aid of Parke, Davis and Company who supplied us with Para-aminosalicylic Acid, and the support of the Mary W. Harriman Fund.

action of serum drawn from normal individuals and patients with pulmonary tuberculosis, following the ingestion of para-amino-salicylic acid on cultures of the tubercle bacillus. The clinical results of PAS are presented in Part II.

Part I—Laboratory Data

Method The organism used in this study was H37Rv although similar results were obtained with other organisms isolated from patients with pulmonary tuberculosis.

Blood was drawn from patients as well as the normal subjects before, and from 1 to 4 hours after, taking the PAS by mouth. The serum was removed and diluted in Dubos media in various concentrations, with a final volume of culture medium of 5 cc. The concentration of serum in the Dubos media ranged from 1:2 to 1:100, the dilution most commonly used being from 1:10 to 1:50. A 7 to 9 day culture of H37Rv in Dubos media was employed, with an inoculum of 0.1 cc, equal to a dry weight of bacteria of 0.01 to 0.02 mg.

Results In the accompanying table (Table I) the inhibitory effects of human serum drawn after ingestion of PAS is demonstrated. It will be seen that control serum had no effect on the growth of the tubercle bacillus, whereas 2 gms of PAS exerted a definite bacteriostatic effect which was more marked with the smaller inoculum, 0.01 mg. This effect was observed in dilutions of 1:10, 1:15, 1:20, 1:30, 1:40 and 1:50. A more striking inhibition, lasting for the full 4 weeks' culture period, is demonstrated as the result of the larger doses, namely 3 to 4 g of PAS.

Transplants made from the serum treated culture tubes showed an inhibition of growth in many instances in fresh Dubos media without additional serum. Considerable variation in these results took place, some tubes finally manifesting a heavy growth at the end of 4 weeks whereas others showed very slight growth.

Experiments were also conducted in which cultures were made with PAS in atmospheres containing 5 to 10 per cent oxygen. Although the growth of the tubercle bacillus in Dubos media was definitely inhibited when placed in atmospheres containing 5 and 10 per cent oxygen, as has been reported with other media previously,⁹⁻¹¹ no additive effect of the combination of anoxia and PAS was observed. No specific effect of increased oxygen concentrations between 40 and 60 per cent on cultures of the tubercle bacillus was noted except that the presence of 100 per cent oxygen exercised a retarding effect on growth for the first week. In earlier studies it has been reported that residence in 50 per cent oxygen atmospheres resulted in prolongation of life of infected rabbits without reduction in the extent of the pulmonary lesions,¹²

whereas exposure to 10 per cent oxygen exerted a retarding effect on the development of tuberculosis in guinea pigs¹³

Lehman has stated that the bacilli in patients who have been treated with PAS do not develop resistance to this drug. In our in vitro studies of para-aminosalicylic acid, a concentration of 0.1 mg per cent in 5 cc of Dubos' media was adequate to inhibit a relatively large inoculum such as 0.02 mg dry weight of the bacteria, when strain H37Rv was employed. A slight growth was manifested in cultures of this organism up to a concentration of 0.078 mg per cent of para-aminosalicylic acid, with complete inhibition at higher concentrations of the drug. A similar response to PAS was observed when other strains of tubercle bacilli were used, isolated from three patients who had not been treated with the drug. In one patient, however, who had received a total dosage of 210 gms of PAS, the organisms tested after treatment were resistant to 2.5 mg per cent, and in two patients, who had received 630 gms and 1000 gms of PAS, the organisms were found to be resistant to 0.63 mg per cent. Although Lehmann³ stated that patients treated with PAS do not develop resistance to the drug, it would appear that strains either way vary considerably in their sensitivity to PAS or that some degree of resistance did develop in three of our patients. To decide this question, the sensitivity of the organism to PAS in vitro should be determined prior to and after each period of therapy.

Although the in vitro studies suggest that this drug is not as powerful a bacterio-static agent as streptomycin, our experiments in animals, including guinea pigs and rats, have also confirmed the reports of others that this drug has a definite retarding effect on the development of experimental tuberculosis in these animals.

Part II — Clinical Data

Methods The dosage of the drug was similar to that employed by Lehmann and his collaborators^{2,4}. Ten to eleven gms were administered in three to five doses daily for three consecutive weeks, with a free interval of one week. One or more courses were given depending upon the tolerance of the patient to the drug. The urine was examined and the serum, non-protein-nitrogen (NPN), was determined before, during and after the completion of one or more courses of PAS. Other routine laboratory procedures, such as sedimentation rate, blood count and chest x-rays, were carried out before and at various periods following administration of the drug.

Results Twelve patients with chronic pulmonary tuberculosis were treated. In five cases the paucity of symptoms of activity rendered estimation of the clinical value of the drug difficult.

INHIBITION OF TUBERCLE BACILLUS CULTURES DUE TO ADDITION OF HUMAN SERUM DRAWN
AFTER INGESTION OF PAS*

Case No	Inoculum H37Rv mg	Dosage PAS gm	Growth with Serum Before PAS	Growth with Serum After PAS				REMARKS
				1 hr	2 hrs	3 hrs	4 hrs	
1 Normal	01	3	++++	0	0	0	0	No growth after 4 wks incubation
2 Normal	01	3	++++	0	0	0	0	No growth after 4 wks incubation
3 Normal	01	3	++++	0	0	0	0	No growth after 4 wks incubation
4 Patient	01	3	No test	0	0	0	0	No growth after 4 wks incubation
5 Normal	01	3	No test	0	0	0	0	No growth after 4 wks incubation
6 Normal	02	2	++++	0	0	0	0	No growth after 4 wks incubation
7 Normal	02	2	++++	++	++	+++	+++	Growth + after 1 wk, ++ after 3 wks, +++ after 4 wks on 2 hr blood
8 Normal	02	2	++++	++	++	+++	+++	Growth + after 1 wk, ++ after 3 wks, +++ after 4 wks on 2 hr blood
9 Normal	02	3	++++	++	++	+++	+++	Growth + after 1 wk, ++ after 3 wks, +++ after 4 wks on 2 hr blood
10 Patient	02	4	++++	+	+	+	+	Growth + after 1 wk, ++ after 3 wks, +++ after 4 wks on 2 hr blood
*Cases 1 through 7 were tested with serum dilutions 1 10 to 1 50, Cases 8, 9 and 10 with serum dilutions 1 5 to 1 15, in Dubos media. One plus, +, indicates slight growth, ++ moderate growth, +++ heavy growth								

EASTLAKE JR AND BARACH

July 1949

These patients are included largely as a demonstration of the lack of toxic effects of PAS, but it was noted that decrease in expectoration occurred in four cases. No serious toxic effects of the drug were noted in any of this group who were in general good health, despite the presence of cavitary tuberculosis.

The remaining seven patients suffered from advanced pulmonary tuberculosis, in an active stage of the disease, with conspicuous symptoms. Streptomycin had been previously employed in four, with a temporary decrease in cough and expectoration, and improvement in general well being. In all of these seven seriously ill patients, decrease in cough and expectoration took place during the first week of treatment. At the end of the first course of three weeks' treatment, cough and expectoration recurred, usually in four days. Following the second and third courses, a progressive diminution of cough and expectoration took place with less tendency for recurrence. The coughing that had formerly manifested itself between arising and retiring was especially reduced. In four of the seven cases in this group, an elevated temperature became normal in a period of four to ten days. In three patients, temporary improvement took place, indicated by decrease in cough and expectoration, with recurrence of symptoms when the drug was terminated. In one far advanced patient, who had intestinal tuberculosis requiring an emergency operation for obstruction, the occurrence of severe nausea and vomiting prevented the administration of more than one course of the drug. This patient died four months after treatment was discontinued.

The case histories of three patients (1, 2 and 3) recited below illustrate the improvement that resulted from administration of para-aminosalicylic acid. The data of the entire group are shown in the accompanying table (Table II).

CASE REPORTS

Case 1 Male, age 37. *History* Known tuberculosis since 1942. Previous treatment included bed rest, phrenic crush and gold therapy. During the six months before admission, the patient suffered from increasing weakness, shortness of breath and, during the last month, from fever and increasing cough. *Physical Examination* Bronchovesicular breathing was heard in both lungs with moist rales in RLLF. X-ray film revealed far advanced bilateral disease, with three cavities in the left lung field and three in the right. The evening temperature prior to treatment reached 101.8 degrees F. *Course* The patient was started on para-aminosalicylic acid at a dosage of 10 grams daily for a continuous period of three weeks, with a free interval of one week between courses. After the first seven days of treatment the temperature was normal and did not again rise above 99 degrees F. The cough was decreased, with reduction in sputum from 1 oz daily to 1½ teaspoonfuls at the end of ten days. The red blood count rose from 3,100,000 to 4,500,000 in one month. The sedimentation

CLINICAL RESULTS OF PARA-AMINOSALICYLIC ACID IN CHRONIC PULMONARY TUBERCULOSIS

TABLE II

6

EASTLAKE JR AND BARACH

July 1949

TABLE II
OF PARA-AMINOSALICYLIC ACID IN CHRONIC PULMONARY TUBERCULOSIS

Case No	Age	Sex	Extent and Nature of Disease	Dosage of Pas Daily No 3 wk Grams Courses	Clinical Results	Side Effects	Remarks		
1	37	M	Far-advanced multiple cavities acute febrile exacerbation	10	3	Temp fell from 101.8° to 99° in 7 days with reduction in cough and decrease in sputum from 1 oz to 1 teaspoonful	No complaints Gained 21 lbs after 3 courses Marked clinical improvement in seriously ill patient		
2	43	M	Bilateral disease with enlarged hilar glands, acute exudative spread to RLL	10	5	3	Temp 103° dropped to 99° after 3 days with reduction in cough	Appetite diminished	Marked clinical improvement with disappearance of exudative lesions on X-ray
3	39	M	Extensive disease in left lung	10	to 12	4	Cough reduced 90% Expectoration reduced 90% Appetite improved	Nausea intermittently	Reduction in cough and expectoration with slight clearing of exudative lesions on X-ray
4	26	F	Bilateral disease apparently arrested, developed positive sputum	10	2	Expectoration was lessened and sputum retained negative on concentration and culture	No complaints	Decreased expectoration in patient In good clinical condition	Nausea forced discontinuance of drug Improvement temporary Previously, temporary improvement with streptomycin
5	52	M	Far-advanced disease on left Intestinal tuberculosis	6	to 8	2	Reduction in cough and expectoration	Severe nausea and vomiting	

July 19

6	33	F	Far-advanced bilateral disease	5 to 10	2½	Cough reduced 70%, sputum reduced 90%	Severe nausea	Nausea forced discontinuance of PAS Temporary improvement took place each course Previously temporary improvement with streptomycin
7	57	M	Disease advanced in left chest with large cavity	11	4	Cough and expectoration reduced 80% on each of the first three courses Less effect on fourth Temp of 100 reduced to normal first 2 courses	Diminished appetite 3 to 4 loose bowel movements daily	Improvement temporary during period of drug administration
8	31	F	Advanced bilateral disease with cavity in LUL	10	1	Cough and expectoration reduced 80% after first week	Nausea and 3 loose bowel movements daily	Temporary improvement comparable to previous course of streptomycin
9	32	F	Moderately advanced disease with cavity in LUL	10	2	Reduction in cough and expectoration	Diminished appetite	Reduction in cough in a patient in good clinical condition with single cavity
10	42	M	Bilateral disease apparently arrested, developed positive sputum	10	1	Slight cough and expectoration almost disappeared in 4 days Sputum retained negative after 1st course	Loss of appetite 2 loose bowel movements daily	Reduction in cough in patient apparently convalescent and arrested
11	53	M	Bilateral disease fibro-productive	10	3	No effect	Decreased appetite Loose bowel movements	Cough slight not affected No change in X-ray after 2 months
12	37	M	Multiple cavities in both lung fields	10	1	Reduction in cough and expectoration in 4 days	Considerable nausea and vomiting	Could not continue drug beyond one course because of vomiting

rate showed no change, 26 mm at the start of the course and 24 mm at the end. The patient experienced a marked increase in general well being and a gradual gain in weight during the first course of treatment. At the end of four courses, i.e., four months, he had gained fifteen pounds in weight. During the fifth month the patient was given one gram of streptomycin daily for three weeks, with continued gradual gain in weight but without significant change in symptoms otherwise. The total weight gained was twenty-one pounds. X-ray film of the chest before and after each treatment showed a gradual clearing of exudative lesions, with decrease in the size of the large cavities in both lung fields and apparent disappearance of two small cavities in the right lung. No planographic x-ray examinations were made. During the period of administration of para-aminosalicylic acid, five determinations of the blood NPN and routine urine tests before and after treatment showed no changes.

The side effects of the drug were absent in this patient, who made no complaints whatsoever during its administration. Six months after treatment the patient had maintained a twenty-one pound weight gain. His dyspnea was improved, and he left the sanatorium for return to England. In this patient with far advanced active pulmonary tuberculosis, the acute symptoms of the disease were promptly controlled with conspicuous and marked clinical benefit. The persistence of multiple cavities in the lung indicate that no arrest of the disease was obtained, nor indeed was it expected in this type of case.

Case 2 Male, age 43 years. *History* Three years before admission while the patient was in the Army, fatigue on slight exertion began. This was soon followed by intermittent fever as high as 104 degrees which became normal after one month's bedrest. There was no cough nor weight loss. X-ray film of the chest at this time revealed dense shadows near the hilum in the right lower lobe and the left midlung field. One examination of the gastric contents was positive for tubercle

CHART I

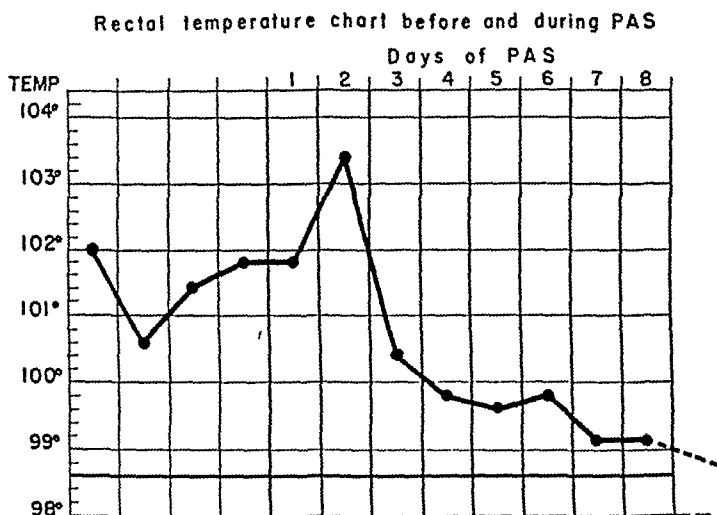


CHART 1 Prompt disappearance of fever after administration of Para-aminosalicylic Acid

bacilli. He was discharged from the Army a year later, the lesions in the lung having shown little change by x-ray examination. The patient was ambulatory, and worked at a desk job. Two weeks before admission he suffered from cough, fatigue and increasing fever. *Physical Examination* Bronchovesicular breathing and inconstant moist rales were heard over the right lower lobe. The fever ranged from 99 degrees F to 103 degrees F. X-ray film of the chest revealed an exudative spread in the right lower lung field, in addition to the dense lesions previously observed. The sputum was negative on smear for tubercle bacilli, but subsequently proved positive on cultures. *Course* Because of the unusual nature of the lesions penicillin was given intramuscularly for a period of eleven days without change in cough or fever. Para-aminosalicylic acid was begun with 10.5 grams being administered daily in five divided doses. The temperature promptly became normal in a period of three days, as shown in the accompanying chart (Chart 1). The cough disappeared on the fourth day of treatment and the patient revealed a marked increase in general well-being. After the first course of treatment, three weeks, the sedimentation rate decreased from 45 mm to 29 mm in one hour. X-ray film of the lungs showed a diminution of the exudative lesions in the right lower lung field, more marked after the fourth course as seen in Figure 1. Two additional courses of para-aminosalicylic acid were given. No changes were observed in the blood count, urine, or blood NPN after each course of therapy. The side effects of the drug in this patient consisted of a decrease in appetite, occasional nausea and a tendency to loose bowel movements. The latter was controlled by administration of one teaspoonful of metamucil morning and night. After a total of six courses of the drug, the patient stopped further treatment for six weeks. Recurrence of fatigue and cough took place. A chest x-ray film revealed an exudative spread at the base of the right



FIGURE 1 a

FIGURE 1 b

Clearing of Exudative Spread after Four Courses of PAS

Figure 1 a X-ray before treatment*Figure 1 b* X-ray after four courses of PAS

lung After three weeks of para-aminosalicylic acid, three grams twice daily, with increased rest, the exudative lesion again disappeared with loss of cough and fatigue

The patient carried on his usual work as a design engineer during the first six months of treatment Despite this activity a tuberculous exudative lesion was brought under prompt control during administration of PAS, recurring when the drug was stopped and again disappearing on treatment with PAS Furthermore, a progressive decrease in what appeared to be hilar lymph node tuberculosis has taken place At this time the patient is cooperating by accepting bed rest and administration of the drug

Case 3 Male, age 39 years *History* Known history of tuberculosis since 1935, arrested in 1938 with reactivity in 1944 Since then the patient suffered from cough and expectoration, with weakness, anorexia and lassitude in year preceding treatment *Physical Examination* Entire left chest was dull to percussion Bronchial breathing with moist rales over left upper lobe was heard The right lung was clear X-ray film showed the mediastinal contents pulled markedly to the left with dense fibrocavernous disease present in the upper lung field *Course* Five courses of PAS were administered, daily dosage 10 grams, each course consisting of three weeks with a free interval of one week During the first ten days of treatment cough and expectoration were reduced 75 per cent There was a considerable improvement in well-being, with increased appetite, despite occasional nausea During the first two months, the x-ray film showed some clearing of exudative lesions in left lower lobe, but no change appeared after this time The patient was referred to a hospital for thoracoplasty which was not thought advisable for him prior to treatment Whereas the patient was formerly constipated, he had one normal movement daily on administration of PAS No effect was noted on the blood NPN, blood counts or urine as a result of administration of the drug

Discussion

Although the series of cases was small, decrease in cough and expectoration was consistently observed Clearing in exudative lesions was noted in three patients, as well as a reduction in elevated temperature to normal No significant change in the size of the cavities of these patients took place, except in one patient in whom it appeared that two small cavities disappeared during the administration of five courses of the drug

The reduction in cough and expectoration was especially noted during the day, occurring in a period of less than one week, with gradual and sustained reduction in symptoms in three cases A feeling of well-being accompanied reduction in cough and expectoration, even in cases in which loss of appetite and intermittent nausea took place The side effects of the drug necessitated discontinuation of treatment in three patients No serious toxic effects were encountered

The most consistent side effect of the drug was diminution

in appetite, which took place in all except two patients. In two others nausea and vomiting were severe enough to cause cessation of the treatment. In six of the twelve patients, two or four loose bowel movements occurred daily, which was counteracted to a considerable degree by the administration of metamucil. In nine patients, determination of the blood NPN was carried out. An elevation was noted in one case with far advanced intestinal tuberculosis, which returned to normal in two weeks. Albumin was noted in the urine in two patients, which disappeared after discontinuing the drug for a few days and did not return when the drug was again administered. Five patients who had an elevated erythrocyte sedimentation rate showed a reduction after the first course of treatment.

Para-aminosalicylic acid would appear to be a therapeutically useful drug in patients with pulmonary tuberculosis, especially those in whom an acute exacerbation of chronic disease has occurred and in whom streptomycin is withheld because of the fear of development of resistance to the latter drug. Despite the statement of Lehmann that resistance does not take place as a result of continued para-aminosalicylic acid therapy, our observations of the concentration of the drug required to inhibit the growth of tubercle bacilli after treatment in three cases suggests that additional investigation is desirable.

Further experience with the drug may result in its administration with fewer side effects. Clinical benefit has recently been observed with a smaller dosage, such as six to nine gms daily. Consideration should also be given to the possibility that smaller amounts of the drug, such as six or eight gms per day, may be useful when combined with other antibiotics, such as promizole and streptomycin.

SUMMARY

The serum of patients and normal individuals after ingestion of 2 to 4 gms of para-aminosalicylic acid produces a definite inhibition of the growth of the tubercle bacillus in Dubos media. This has been demonstrated with the H37Rv strain as well as with strains recovered from patients with active pulmonary tuberculosis.

Para-aminosalicylic acid was administered to twelve patients with advanced chronic pulmonary tuberculosis. The dosage employed was 10 to 11 gms daily in courses of three weeks, with a free interval of one week. In seven patients in whom the symptoms of active infection were sufficiently marked to permit judgment of the effectiveness of drug, observable clinical improvement took place in all. In three patients recurrence of symptoms on cessa-

tion of treatment took place. Three patients who suffered from fever and signs of acute exudative tuberculosis were much improved and in good general condition after treatment, but without arrest of their disease.

The characteristic effects of administration of para-aminosalicylic acid were prompt reduction in cough and expectoration, and decrease in fever when present. These favorable results were generally manifested within the first week of treatment. The side effects of the drug were intermittent nausea, vomiting and looseness of the bowels. In three of the twelve patients these symptoms were sufficiently severe to force discontinuance of the drug.

The favorable clinical results of treatment with para-aminosalicylic acid in chronic pulmonary tuberculosis suggests that this drug is a useful agent in the treatment of acute exacerbation of the disease.

The possibility that administration of para-aminosalicylic acid with other antibiotics, such as promizole and streptomycin, would appear to deserve investigation.

Since this paper was written, PAS has been administered in one or more courses to ten additional patients with chronic pulmonary tuberculosis. Clinical improvement took place in all instances, characterized especially by reduction in cough and expectoration and improvement in well-being. Side effects were few on a dosage of 3 gms. three times daily. A favorable clinical response was also noted in patients who had become resistant to streptomycin. In the treatment of cavitary pulmonary tuberculosis by lung immobilizing therapy in the equalizing pressure chamber, closure of cavity has taken place in a number of cases of advanced and moderately advanced tuberculosis,¹⁴ in a few cases recently treated by this method PAS has been added in the hope of shortening the time required for cavity closure.

RESUMEN

El suero de pacientes y de individuos normales que han ingerido de 2 a 4 gramos de ácido para-aminosalicílico produce una inhibición bien definida del crecimiento del bacilo tuberculoso en el medio de Dubos. Se ha demostrado esto con la cepa H37Rv y también con cepas obtenidas de pacientes con tuberculosis pulmonar activa.

Se administró el ácido para-aminosalicílico a doce pacientes con tuberculosis pulmonar crónica avanzada. La dosis empleada fue de 10 a 11 gramos diarios en series de tres semanas, con un intervalo libre de una semana.

En siete pacientes en los que los síntomas de infección activa fueron lo suficiente marcados para permitir que se formara un juicio acerca de la eficacia de la droga, tuvo lugar mejoría clínica.

observable en todos ellos En tres pacientes tuvo lugar recrudecimiento de los síntomas al pararse el tratamiento Tres pacientes que tenían fiebre y signos de tuberculosis exudativa aguda quedaron muy mejorados y en buena condición general después del tratamiento, pero sin estacionárseles la enfermedad

Los efectos característicos de la administración del ácido para-aminosalicílico fueron la pronta reducción de la tos y la expectoración y la disminución de fiebre cuando existía Por lo general se manifestaron estos resultados favorables durante la primera semana del tratamiento Los efectos laterales de la droga fueron náusea intermitente, vómitos y diarrea En tres de los doce pacientes fueron estos síntomas lo suficiente severos para obligar que se descontinuara la droga

El favorable resultado clínico del tratamiento de la tuberculosis pulmonar crónica con el ácido para-aminosalicílico sugiere que esta droga podrá ser un agente útil en el tratamiento de las exacerbaciones agudas de la enfermedad

La posibilidad de administrar el ácido para-aminosalicílico con otros antibióticos, tales como el promizol y la estreptomina, parecería merecer investigación

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Streptomycin in Tuberculosis, Clinical Experience*

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Summary

1) Seventy-seven cases of tuberculosis have been treated, presenting various clinical pictures with varying complications and foci of localization. Of the total, 66 cases have been analyzed with the following results: 33 have finished the treatment, 17 are continuing, 8 have been discontinued, and 5 have died.

2) All of the patients were under treatment in the sanatorium. The diagnosis was substantiated in each case by finding tubercle bacilli in the respective specimens. Sixty-six per cent of all patients who completed the treatment have gained weight, some as much as 18 Kg. Favorable changes have been noted in the temperature curves, and in some cases the curve has returned to its original contour regardless of its initial shape. Tuberculin skin sensitivity, which was negative at the onset in 5 cases, turned positive during the 30 days of treatment.

Bacteriologic studies showed a marked decrease in the excretion of bacilli, and conversion occurred in 15 cases. The changes in the sedimentation rate were consistent with the clinical improvement. In almost all cases, regardless of the final outcome, marked detoxification was observed, with remission of functional symptoms, improvement of appetite, and typical euphoria.

3) Aside from its favorable effect on recent exudative lesions, streptomycin is offered as a form of chemotherapy for tuberculous exacerbations.

4) In conjunction with accepted rational therapy and insulin, it has proved effective in exudative flare-ups of pulmonary tuberculosis in diabetics.

5) In the treatment of pulmonary tuberculosis in pregnancy, streptomycin has proved effective. Pregnancies have been carried to term successfully with normal deliveries and with evident improvement in the pulmonary lesion of the mother. The dosage in

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these cases should be moderate, and toxic reactions in the mother do not necessarily warrant discontinuation of the treatment. It seems that the greater resistance of the fetus, or its greater tolerance for the drug, are due to the higher alkalinity of the fetal blood.

6) In the early stages of tuberculous empyema when the pleurae have not been appreciably damaged, it is permissible to use the intramuscular route alone with conventional drainage procedures performed at the proper time. In more advanced cases of frank empyema, one should employ proper drainage and obliteration of the pleural cavity by phenicotomy or thoracoplasty in conjunction with streptomycin.

7) In cases of recent dissemination treatment should be started as early as possible. Persistence of the radiologic findings with an improvement in the clinical picture should be sufficient indication for institution of proper collapse therapy according to the case.

8) Cases of tuberculous laryngitis and tracheobronchitis derive considerable benefit from streptomycin. The intramuscular route is preferred in these cases. Aerosols have not proved as effective as was anticipated, hence, if employed, should always be used in conjunction with intramuscular administration. Apparently complete cures of tuberculous laryngitis have been obtained in cases of hematogenous tuberculosis.

9) Acute, subacute, and chronic hematogenous pulmonary tuberculosis and their extrapulmonary localizations are definite indications for streptomycin therapy which should be started without delay as soon as this diagnosis has been established. Improvement of lesions associated with hematogenous pulmonary tuberculosis has been observed in the following foci: testes, joints, pleurae, kidneys, and superficial lymph nodes.

10) In cases of tuberculous enteritis associated with various types of the disease, treatment has been successful in alleviating all the symptoms, and in some cases even regression of the radiologic picture has been noted. In others, radiologic evidence of cicatricial involvement is still present. As yet, we cannot state that healing of the enteric lesions is definite until a longer follow-up study of the patients has been carried out.

11) Twenty-eight of the patients have shown no reactions to the drug. Eight had local reactions, and 12 had reactions of an allergic nature. Of these 12, seven had appreciable febrile reactions, three had urticaria, one a morbilliform exanthema and one a maculopapular exanthem. This latter presented a problem of considerable importance because the reaction produced an exanthem and the patient could not be fed properly. In addition, this patient had hemorrhagic infiltrations in the palms. In seven cases

the drug produced nausea and vomiting. Two showed alterations of the renal function in the form of oliguria. The complete vestibular syndrome has not been observed in any case, but fourteen had headaches with or without nausea and vomiting, and five have complained of dizziness and mild vertigo. As for hearing capacity, three have had tinnitus with slight hypacusia, and one had transient hyperacusis. One case had marked somnolence and another had joint pains.

The best results have been obtained with the following indications:

- (1) Any superficial mucosal lesion in the mouth, larynx, bronchi, or intestines
- (2) Any localized lympho-glandular lesion, especially when there is spontaneous drainage
- (3) Any case of hematogenous dissemination, especially pulmonary, but also less effectively, of extrapulmonary origin
- (4) In the lung, any perifocal reaction, or any specific recent exudative reaction, regardless of the route of dissemination

This summary is presented as evidence of the interest with which we have used and studied streptomycin, and is offered as our modest contribution to the voluminous statistical data of American clinicians.

Extrapleural Pneumonolysis with Plombage Versus Thoracoplasty

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Thoracoplasty has always been one of our most reliable operative procedures in the surgical treatment of pulmonary tuberculosis and although the disadvantages of this operation are numerous, it still yields the highest percentage of sputum conversions and cavity closures Throughout the surgical literature the procedure of extrapleural pneumonolysis with various "plombe" materials¹ is encountered as a rival to thoracoplasty and its exponents compare its capabilities as a collapse procedure with this latter operation Certainly it obviates the objectionable features of thoracoplasty and from a theoretical standpoint should produce as satisfactory an end-result

It is interesting to observe how optimistic many authors were regarding the results obtained with the extrapleural operation as employed in selected cases²⁻¹² In the following tabulation the various advantages for extrapleural pneumonolysis with plombage over thoracoplasty are enumerated with notations as to the various exponents of each advantage

- 1) Expectoration made easier preventing aspiration pneumonia,^{2 4 9 10 13 14}
- 2) Cosmetic effect—no deformity,^{4 10}
- 3) Selective collapse with maximum preservation of normal pulmonary parenchyma and respiratory function,^{4 9 15 18}
- 4) Abnormal conditions for heart and lungs not produced as with thoracoplasty,^{2 4}
- 5) Reduced possibility of paradoxical respiration as seen in thoracoplasty,^{4 9}
- 6) Bilateral lesions are no contraindication to it,^{9-11 13 15 17 19}
- 7) Only one operation is necessary,¹⁰
- 8) Thorax maintains its function,^{2 18}
- 9) Results are immediate⁴

Although many early authors praised extrapleural pneumon-

*From the Department of Medicine and Surgery, Veterans Administration, Oteen, North Carolina, published with permission of the Chief Medical Officer, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors

olysis regardless of the type of pack employed, the majority made the reservation that extrapleural packing should be used only in selected cases, and that it was inferior to thoracoplasty Baer^{4 5} stated that pneumonolysis with pack was a worthy substitute for thoracoplasty in selected cases, and deWinter and Sebrechts⁶ and Winternitz¹⁵ actually considered the operation superior to thoracoplasty when indications were closely adhered to, and substituted it for thoracoplasty in such cases Aufses¹⁶ in 1929 stated that extrapleural pneumonolysis was never indicated as a substitute for thoracoplasty and that up to that time no known method of extrapleural stripping with plombage had withstood careful investigation He summarized his article by affirming that the procedure of extrapleural pneumonolysis is useful in only an occasional case of pulmonary tuberculosis and that the percentage of failures was so high that he questioned the usefulness of the operation

We agree with Aufses so far as the usefulness of the operation is concerned, and our results have clearly demonstrated that the procedure is never superior to thoracoplasty As to its use in selected cases, or in cases with precise indications where thoracoplasty is contraindicated, we feel that the majority of patients would be far better off without any major collapse procedure rather than undergo an extrapleural pneumonolysis with any form of plombe material including lucite, air, or gomenol

In the past two years we have performed 14 operations of extrapleural pneumonolysis with lucite plombage as primary major collapse procedures In each of these cases indications for the procedure were closely followed and were considered optimum for the procedure Of these, four patients, or 27.1 per cent, converted their sputum Eight, or 57.1 per cent of the lucite packs have had to be removed because of complicating factors Fortunately the mortality rate has been zero

During the past five years our department has performed 1,128 stages of thoracoplasty upon 415 patients The mortality rate has averaged 0.75 per cent per operation The sputum conversion rate with the far advanced, often bilateral type of lesion which we accepted for operation averaged 65 per cent

These figures show that our percentage of sputum conversions and cavity closures has been low in the patients treated with extrapleural pneumonolysis with lucite pack, and complications have been numerous The procedure has been abandoned on our surgical service and it is felt that all of the lucite packs still *in situ* will have to be removed during the next few months A comparison of these results with those obtained through thoracoplastic procedures demonstrates that thoracoplasty still remains our most reliable collapse method of treatment

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Pneumoperitoneum Therapy in Lower Zone Tuberculosis

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The treatment of pulmonary tuberculosis has been and is a complex problem. In general, rest has been advocated as a beneficial measure in cases with clinical or radiological activity. Unfortunately, rest alone is not usually effective except in limited disease without cavitation. As the lesion of pulmonary tuberculosis becomes established, the picture becomes complicated. Adhesions of the pleura often are responsible for mechanical limitation of the respiratory function of the involved lung. Furthermore, fibrosis is a very frequent major complication producing distortion of the mediastinum and its contents, also fibrosis may be diffuse up-setting the normal physiology of gaseous exchange through the pulmonary alveoli. Many cases in response to immunological phenomena peculiar to infection with tubercle bacilli show either localized or extensive caseation.

Before one attempts to outline a course of treatment for a case of pulmonary tuberculosis, an intensive investigation of the patients as a whole is desirable. Let us for simplicity's sake consider that we are dealing with a group of patients whose only problem is that of pulmonary tuberculosis. We must then, first of all, get a picture of the activity of the case. Are the lesions progressing or regressing? To what extent has pulmonary fibrosis progressed? If there is extensive fibrosis, is there adequate absorption of oxygen and elimination of CO_2 ?

One must also attempt to evaluate the degree to which the pleura has been involved. Here the history of pre-existing pleurisy is important. Further studies might include bronchspirometry. In those cases in which the pleura is radiologically thickened the problem is straightforward. It is necessary definitely to determine the location, size and character of pulmonary cavities which may be present. Peripherally placed lesions collapse with greater regularity than those more medially situated. Is it an atmospheric, positive, or negative pressure type of cavity? Are the walls of the cavity hard, or soft, is the cavity situated in soft collapsible lung, or is there extensive adjacent fibrosis? A further consideration is that lower zone cavities in tuberculosis are frequently in the apex of the lower lobe. This location is of course

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central As has already been stressed relaxation of centrally placed pulmonary tissue is not maximum

There are several mechanical methods of treatment for pulmonary tuberculosis with cavitation advocated to date In 1931 Dr Banyai made a new step in the therapy of pulmonary tuberculosis He used and widely advocated the introduction of air into the peritoneal space As is well known the intrapleural pressure is negative The pressure in the peritoneal space is neutral, except in the subdiaphragmatic region where it is negative Suspended between these two pressures is the diaphragm It is obvious then that to increase the abdominal pressure would favor an elevation of the diaphragm Obviously a point against this therapy is that there is bilateral elevation of the diaphragm In an attempt to give more selective collapse, numerous workers have advocated phrenic interruption on the desired side This has been very effective, often increasing the elevation of the involved diaphragm by 2 to 8 cm Since the original paper of Dr Banyai, many articles have been published and it is the opinion of most workers that lower and mid zone lesions have responded more favorably than those higher placed

Here then is a form of therapy which appears peculiarly suited to disease involving the lower and mid zone of the lung The therapy of lower zone tuberculosis is generally considered far from satisfactory As we have already mentioned, thoracoplasty is best suited to upper zone disease A limited lower thoracoplasty is technically an unsatisfactory procedure To use the orthodox thoracoplasty which collapses the lung from above downwards is a wasteful procedure in that healthy lung is unnecessarily defunctionalized If the lesion is high in the lung, pneumothorax is often beneficial but here again considerable good lung is put out of order in an attempt to effectively collapse the lower zone Also, pneumothorax is far from innocuous All who have used this procedure know the frequency of adhesions which require division, this is often impossible and in the others pleural effusion and empyema are by no means uncommon Even in the technically successful pneumothorax we are often left with a crippled lung due to pleural thickening

On the other hand, pneumoperitoneum is a relatively safe and easy procedure There is no absolute location at which this must be done It seems however that it should not be done over the liver as it has been shown that here puncture of the liver may easily be the cause of an air embolism Also it is doubtful whether the right lower abdominal quadrant should be used, as here the possibility of adhesions from appendiceal inflammation is obvious It has been mentioned that puncture of the bowel may com-

plicate pneumoperitoneum This has been very rare However, if the bowel were adherent to the peritoneum at the site of induction, it most likely would occur Thus most workers induce pneumoperitoneum on the left side Initially 400-700 cc of air are given The amount is largely determined by the size of the patient and the objective symptoms which the patient presents If too much air is given there is usually referred diaphragmatic pain in the shoulders In maintaining the pneumoperitoneum, air is given periodically at approximately weekly intervals, usually 800-1000 cc Here again the patient's comfort is the chief point in fixing the quantity to be given Usually in a short period of time the patients are asymptomatic following pneumoperitoneum Occasionally individuals complain of anorexia, this is thought to be due to dislocation of the stomach and bowel Anorexia can usually be obviated by proceeding with therapy in a cautious manner Peritoneal adhesions are occasionally seen, but these do not appear to affect either the treatment or the effectiveness of the procedure A few cases have been observed where peritoneal effusion has followed pneumoperitoneum This has not appeared to effect the patients progress and is usually not considered to contraindicate continuation of therapy No doubt, peritoneal effusion occurs in those who have tuberculous involvement of their peritoneum It is interesting to note here that numerous workers feel that air injection into the peritoneal cavity is beneficial in cases of tuberculous peritonitis A point which seems important to us is that there is little possibility that we will produce a crippled lung as so frequently occurs in pneumothorax because here the pleura is not affected



FIGURE 1

FIGURE 2

Fig 1 There are abnormal shadows in the right lower chest with cavitation laterally and below the right hilus—*Fig 2* A phrenic crush has been done on the right side, giving more selective collapse on this side



FIGURE 3

Fig 3 There are abnormal shadows in the right base with a large cavity just below and lateral to the right hilus. On the left side, there are abnormal shadows in the 2nd interspace anteriorly laterally placed.—*Fig 4* Pneumoperitoneum has been induced. There is a good rise of the right diaphragm associated by a phrenic crush right. There is a new area of parenchymal disease in the right upper zone complicated by cavitation. There is regression of the disease on the left side.—*Fig 5* Pneumothorax is induced on the right side with obliteration of the upper zone cavity. Pneumoperitoneum is being maintained. Pneumothorax on the right side has been abandoned. The lesion on the left side becoming more fibrotic in nature.

FIGURE 4

FIGURE 5

CASE REPORTS

D P was admitted to the hospital on June 15, 1946. The duration of disease was indefinite. He was in good physical condition, afebrile and his pulse was regular and normal. Examination of the chest revealed only dullness over the right base posteriorly. Radiologically there was moderately advanced exudative pulmonary tuberculosis, involving the right lower lobe. There were two small cavities at the apex of the right lower lobe, visualized most clearly by tomographic studies (Fig 1).

In this case it was felt that pneumoperitoneum offered the best chance of arrest of the disease. Pneumoperitoneum was started in July 1946 and a right phrenic crush was done on July 25, 1946. His sputum decreased in amount from 1 ounce to drachms 2 daily. It is interesting to note that while in this hospital no positive sputums were obtained on this patient, prior to induction of pneumoperitoneum. However, sputum examination done a month prior to admission showed that his sputum was positive for tubercle bacilli. Following induction of pneumoperitoneum, there has been good relaxation of the lower half of the right lung (Fig 2). His sputum has remained negative to date, eight months after establishment of treatment.

Patient's clinical condition has remained satisfactory. His weight has been maintained. He is afebrile, pulse continues normal. Haematological studies indicate that there has been diminished activity, there being now a low sedimentation rate and the white blood count only slightly above normal.

M I was admitted to this hospital on August 1, 1944. On admission patient was found to be underweight. Her blood pressure was normal. Her abdominal examination showed no abnormality. Her genito-urinary system appeared to be within normal limits. Examination of her chest showed bilateral pulmonary tuberculosis with a giant cavity in the right lower lobe and soft parenchymal lesions in the left apex and left infra-clavicular region (Fig 3). On admission, sputum was Gaffky 5. In this case pneumoperitoneum was done and this was made more selective by doing a phrenic crush on the right side on October 13, 1944 (Fig 4).

Shortly after the institution of this treatment, the cavity in the right lower lung diminished in size and over the succeeding four months the cavity gradually disappeared, being no longer demonstrable either clinically or radiologically. Coincident with the radiological disappearance of the cavity in the right lower zone, sputum became negative for tubercle bacilli.

In August 1945 it was noted that there was cavitation in the right apex and effectively to collapse this area, a pneumothorax was induced on the right side in November 1945 (Fig 5). The collapse was satisfactory and there was obliteration of the cavity in the right upper zone. Progress in this case has been good. Temperature has remained afebrile and sputum has been consistently negative since the latter part of 1944. In this case atelectasis of the right lower lobe developed as a complication shortly after the initiation of treatment. This atelectatic lobe was observed, and it was found that a minimal degree of bronchiectasis developed, but this was not a complicating factor in the disease, as there was no excessive expectoration of sputum and there were no signs of infective episodes. Bronchoscopy revealed an apparently normal bronchial tree, except for some submucous granulation in the right lower lobe bronchus proper.

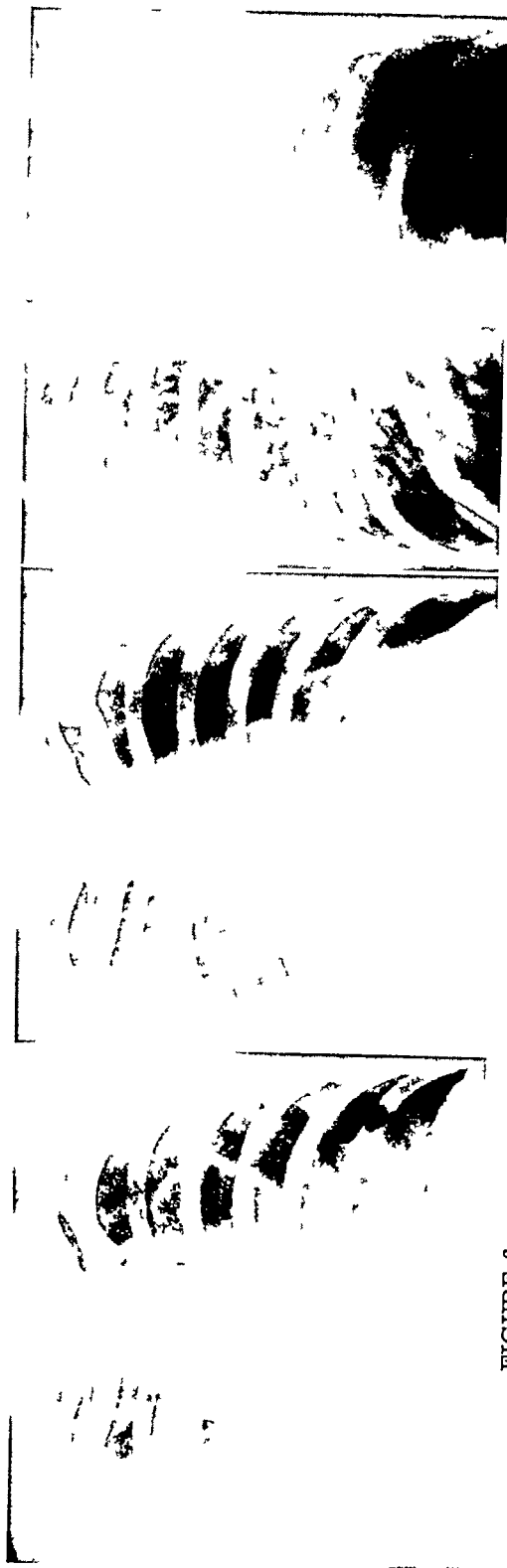


FIGURE 6

Fig 6 There is a pneumothorax present with approximately 50 per cent collapse. Pneumothorax is complicated by an adhesion in the upper part. There is a large inflated cavity in the mid zone of the collapsed lung. —*Fig 7* The adhesion present in figure one has been divided. There is now approximately 75 per cent collapse of the left lung. The cavity is still present but considerably reduced in size. —*Fig 8* Pneumothorax has been abandoned. There is a considerable rise of both halves of diaphragm. The left diaphragm is considerably higher than the right, due to the phrenic crush on the left. The left lung is partially obscured by pleural reaction. The cavity however is not visualized.

FIGURE 7

FIGURE 8

During the period of subsequent observation, her sputum has been persistently negative and there has been progressive resolution of the densities in both lungs

J C was admitted December 4, 1944 On admission patient showed a moderate degree of wasting Temperature was normal There were no signs of physical abnormality, other than in examination of the chest which showed dullness at the left apex posteriorly, with scattered rales in this area There were signs of a pneumothorax on the left side X-ray film of the chest showed a 50 per cent collapse of the left lung by pneumothorax Pneumothorax was inefficient due to an adhesion and there was a large tension cavity present in the upper half of the left lung (Fig 6) Bronchoscopy, January 1945, revealed tuberculous bronchitis

In November 1944 a pneumonolysis was done on the left side and there was a good collapse of the left lung (Fig 7), however, the cavity was still present, although somewhat diminished in size Shortly after pneumonolysis, patient developed extensive pleural effusion on the left side and it was thought inadvisable to continue pneumothorax Pneumothorax was allowed to re-expand and the fluid was aspirated from the left chest In May 1945 a phrenic interruption was carried out on the left side and this was followed by the induction of pneumoperitoneum in July 1945 There was almost immediate obliteration of the cavity present in the left upper lung (Fig 8) Patient has been observed from this date to March 1947 and has shown a persistent normal temperature with normal pulse Weight has increased 30 pounds Haematologically there are no signs of activity Sputum has remained consistently negative since May 1945

G F was first diagnosed as suffering from pulmonary tuberculosis in 1941 in a Tuberculosis Clinic in this city Bed rest was carried out for seventeen months at home without any appreciable improvement in the pulmonary condition In April 1946 patient was admitted to hospital for further treatment

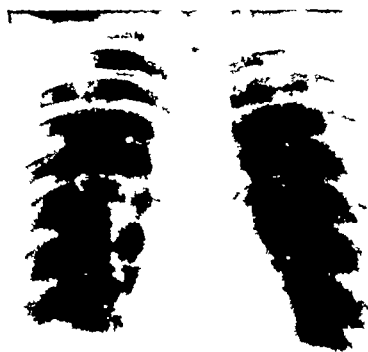


FIGURE 9



FIGURE 10

Fig 9 Tomogram 6 cm from the skin of the back shows a large cavity in the right hilar region—Fig 10 Pneumoperitoneum has been established and a phrenic crush has been done on the right Note the rise of both halves of the diaphragm greater on the right There is good relaxation of diseased area There are also lesions in the upper portion of the left lung

Physical examination showed a well developed, well nourished girl with normal temperature and normal pulse. There was no sputum and gastric lavage was negative. The examination of the lungs showed a clear left lung. On the right side there were moist rales and bronchial type of breathing over the upper portion of the right chest. Radiologically, there were signs of soft parenchymal lesions above the 2nd rib anteriorly on the left, and near the right hilus there was a large cavity with soft parenchymal lesions throughout the right lower lobe (Fig 9). In spite of the negative sputum on admission there was no doubt as to the etiology of this disease, as the patient had previously been proven to have positive sputum. Consequently, an attempt was made to obliterate the cavity in the right hilar region by pneumoperitoneum and a phrenic crush on the right side, this treatment being initiated in May 1946. There was a very satisfactory rise of both halves of the diaphragm, greatest on the right, and there has been radiological disappearance of the cavity in the right hilar region (Fig 10). The lesion in the left apex has remained stationary.

Clinical progress has been good. Temperature ran a low subfebrile course until January 1947, ten months after institution of collapse therapy. Temperature, however, has been normal for the last three months. Patient has no sputum and repeated gastric lavages have been negative both by smear and culture. There has been persistent obliteration of the cavity in the right hilar region. Weight is being maintained satisfactorily.

CONCLUSIONS

- 1) Pneumoperitoneum is a safe and simple procedure.
- 2) Excellent collapse of the lower 2/3 of the lung can be achieved by this means.
- 3) An added phrenic nerve interruption gives more selective collapse of the diseased side.
- 4) Duration of pneumoperitoneum treatment is an unestablished factor, but it seems that it should be maintained as long as one would a pneumothorax.
- 5) Cases are presented which demonstrate the effectiveness of this therapy.

CONCLUSIONES

- 1) El neumoperitoneo es un procedimiento salvo y sencillo.
- 2) Por este medio se puede obtener un colapso excelente de las dos terceras partes inferiores del pulmón.
- 3) La adición de la interrupción del nervio frénico da un colapso más selectivo del lado afectado.
- 4) No se ha establecido todavía la duración de la neumoperitoneoterapia, pero parece que se debería mantener por un tiempo igual al que uno mantendría un neumotórax.
- 5) Se presentan casos que demuestran la eficacia de esta terapia.

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Carcinoma of the Lung with Nonmalignant Pleural Effusion Recovery by Pneumonectomy*

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One of the universally accepted contraindications to operability of a primary bronchiogenic carcinoma of the lung is the presence of metastatic pleural effusion. Such effusions occur in approximately 11 to 15 per cent of all bronchiogenic carcinomata.

Diagnosis of metastasis to the pleura is made by the finding of tumor cells in the fluid. The usual method for the study of tumor cells is that of Mandelbaum,¹ in which the fluid is centrifuged down and a sediment obtained, which, after hardening with formalin, is treated as ordinary tissue and stained with hematoxylin and eosin. The addition of glacial acetic acid to the fluid to bring the acid to 2 per cent is recommended by Foot² in order to prevent coagulation. By the Mandelbaum method, approximately 60 per cent of pleural effusions due to malignancy will show tumor cells. The remaining 40 per cent are missed for the following reasons: (1) Single tumor cells may be difficult to differentiate from the cells of long standing transudates. (2) The tumor may not shed cells. (3) The fluid is a transudate due to venous obstruction by a tumor mass. When, therefore, tumor cells are not seen in effusions associated with carcinoma of the lung, it is logical to assume that the fluid is in the 40 per cent group and that the patient therefore has a metastatic effusion. As a result, it has been generally accepted that the presence of any fluid, whether it is serous or bloody, is a contraindication to operation.

That pleural effusion due to causes other than malignancy may occur in patients with bronchogenic carcinoma is exemplified in the following case:

V.D., age 50. Entered the Jewish Hospital on June 30, 1943 and was discharged on August 23, 1943. The patient had a gradual onset of a chronic productive cough starting 1½ years ago. The cough became worse about six months prior to admission to the hospital at which time he began to lose weight. One week prior to admission he began to have chills, fever and dyspnea.

Physical Examination. Temperature 101 degrees F, pulse 76, respiration 24 per minute, blood pressure 108/68. The patient was a thin emac-

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iated white male who looked chronically ill. He was well oriented. The important physical findings were diminished expansion of his left chest, diminished tactile fremitus, dullness to flatness posteriorly from the angle of the scapula downward. Breath sounds were vesicular elsewhere. In the right base there was a moderate number of coarse rales.

Laboratory Findings RBC 3,510,000, WBC 13,000, Hgb 69 per cent. Differential blood count, normal. Urine, negative. Sputum, purulent, showed no pneumococci, fungi or acid-fast bacilli. Roentgenogram of the chest revealed a shadow obliterating the left costophrenic angle, interpreted as pleural effusion.

From the left pleural space 1500 cc of sero-sanguinous fluid was removed with considerable improvement of the patient's dyspnea. The fluid had a specific gravity of 1018, was sterile on culture, showed no bacteria on direct smear and a section sediment showed numerous polymorphonuclears and solid-staining cells with eccentrically placed nuclei. No tumor cells were seen. Another aspiration obtained 400 cc of a similar fluid and again the sediment showed no tumor cells. Fluoroscopy following the thoracentesis revealed collapse of the left lower lobe previously hidden by the fluid. Bronchograms showed obstruction of the



FIGURE 1 Bronchoscopic biopsy of left lower lobe showing squamous cell carcinoma

left lower lobe bronchus and bronchiectasis of the right lower lobe. Bronchoscopy revealed the left lower lobe bronchus completely obstructed by a hard cauliflower growth. Section showed a squamous cell carcinoma (Fig 1). The patient was given a course of sulfadiazine which apparently lowered his fever and on July 13, 1943 a left pneumonectomy was performed by Dr J L Mudd. The pleural cavity showed no evidence of metastasis. The lung showed atelectasis of the left lower lobe. On opening the bronchus, a mass could be seen obstructing the lumen and extending down the bronchus for a considerable distance. The bronchi

beyond the point of obstruction were dilated and contained a large amount of yellowish pus. On cut section, the lung tissue appeared quite compact and contained numerous small abscesses.

Microscopic section through the tumor mass showed erosion and replacement of the bronchus by a group of large polygonal cells, varying in size but fairly well differentiated. The tumor had grown in small sheets, some of which were necrotic in the center. There was invasion of the underlying lung with marked infection and fibrosis. The pleural surface of the lung showed no tumor invasion. The alveoli throughout showed large phagocytic cells. The left upper lobe was negative. No evidence of carcinoma was seen in the tracheo-bronchial nodes. Section through an additional resection of the bronchus following pneumonectomy revealed no evidence of malignancy.

One month following the operation, the patient developed empyema as a result of the bronchial stump opening. Thoracotomy was performed and because of the persistent drainage, thorocoplasty was done and completed in January of 1944. He had one severe episode of a pneumonitis of the right lower lobe, apparently associated with his right lower bronchiectasis which was present prior to the operation. This cleared up promptly following bronchoscopy. In August, 1944 a diagnostic bronchoscopy was done and the entire tracheobronchial tree was clean. A recent examination showed no evidence of recurrence of the malignancy. He was well five years after operation. The only symptoms are moderate cough and sputum due to the bronchiectasis of the right lower lobe bronchi.

The pleural effusion in this patient was an inflammatory one. It is well known that hemorrhagic effusions may be due to infection with pyogenic micro-organisms. In Berliner's⁶ series, 65 per cent of hemorrhagic effusions were due to malignancy and 11 per cent to inflammations of various types. It is obvious that a patient with bronchiogenic carcinoma may develop pleural effusion due to secondary atelectasis and infection, and that this effusion is nonmalignant.

SUMMARY

A 50 year old man with proved bronchiogenic carcinoma of the lung had a large hemorrhagic pleural effusion. Study of the fluid showed no tumor cells, but evidence of inflammation. A pneumonectomy was performed and the fluid was shown to be due to secondary pneumonitis. The patient is well after five years post-operatively.

The presence of pleural effusion in cases of bronchiogenic carcinoma of the lung does not contraindicate operation unless there is unmistakable evidence of metastasis to the pleura such as tumor cells in the fluid or visible tumor in the pleura.

RESUMEN

Un hombre de 50 años de edad con carcinoma pulmonar broncogénico comprobado, tuvo un considerable derrame pleural he-

morragico El estudio del derrame no demostró células de tumor, sino signos de inflamación Se ejecutó una neumonectomía y se demostró que el derrame fue causado por neumonitis secundaria El paciente esta bien cinco años después de la operación

La presencia de derrame pleural en casos de carcinoma broncogeno del pulmón no contraindica la operación a menos de que existan signos indudables de metástasis a la pleura, tales como celulas de tumor en el derrame o tumor visible en la pleura

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Nutrition Education in Institutions Caring for Tuberculous Patients

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Introduction

Food has always been considered of basic importance in the treatment of tuberculosis. In spite of this, apparently very little systematic effort has been put forth to make the patient conscious of this fact except in those instances when extreme or faddish practices have been recommended.

Nutrition education appears to have been left to chance while the patient was being treated for tuberculosis, according to information gained through individual conferences with clinic and hospital patients and through home visits with nurses during the past five years. A frequent comment made by these patients was "The doctor told me I could go home and lead a normal life." Psychologically this was good advice, but how many of the doctors knew what was "normal life" for his patients, especially when it came to eating? Too often professional people assume that the general population has more information on this topic than it really has. Furthermore practice does not necessarily coincide with knowledge.

A study of the dietaries of 100 patients interviewed in three of the Institute Chest Clinics in Cook County in 1947 revealed that a small percentage of them included the protective foods regularly in their meals. Not one of the arrested cases or their families reported that he had been given any specific instruction regarding his eating habits during the period of treatment. A few had "picked up" and asked for information because they observed that certain foods were served to them regularly while they were in the institutions. One woman had become interested enough in her own food intake to attend nutrition classes given in her community.

Opportunities for Nutrition Instruction

To give the patient an understanding of what food does for him both in sickness and in health, the following methods are available

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(1) The individual conference is probably the most effective. It is then the patient realizes that someone has a personal interest in him and can help with his particular problems. This is essential to his emotional as well as his physical well being. This method, however, is time consuming, and with the limited staff in most tuberculosis hospitals may not be practical.

(2) The second way to reach a number of patients for educational purposes is to meet with them in small groups, offering all a chance for discussion. The groups need not be large but should be composed of a sufficiently large number to keep the conversation interesting and in useful channels. This method also presupposes that the patients are ambulatory.

(3) The third method for educating patients is the use of literature and visual aids. These must be carefully chosen. Literature should be colorful and easy to read. It must have facts stated simply yet interestingly. Posters should be meaningful and attractive and movies must be timely as well as informational. Though these materials are valuable in teaching patients, their greater contribution is probably that of supplementing and reinforcing the spoken word.

Nutrition Education Programs in Practice

Just how much is done in tuberculosis hospitals to help the patient to have an appreciation of the foods served to him? Because certain impressions regarding nutrition education programs in institutions caring for tuberculous patients had been formed through conferences with the aforementioned patients and their families, it seemed that specific information should also be secured from the other side, namely the sanatorium. A plan was made therefore to study the activities involving nutrition in some of the tuberculosis hospitals and sanatoria in the United States. A brief description of this study is presented.

A two page questionnaire was prepared in cooperation with the statistical section of our organization which when filled out, would give the greatest amount of information, yet demand the least time and effort on the part of the staff members of the institutions who would have to fill them out.

Since this organization is located in the middle western group of states, questionnaires were sent to *all* the tuberculosis hospitals in Minnesota, Wisconsin, Iowa, Illinois, Indiana, Michigan and Ohio. In order to have a larger number and to secure some data for comparison of practices in other parts of the country, copies were also sent to *all* such institutions in Pennsylvania, New York, Colorado and California, and to those under Federal and State control in the remaining states.

Though there are numerous occasions during the course of hospitalization when one might learn of the patient's eating habits and discuss food and nutrition with him, the most obvious times have been recorded and evaluated. These are (1) Upon admittance, when the history and general information are secured (2) During hospitalization, while collecting and studying dietary records (3) In making ward rounds when general conferences may be had with the patient (4) In organized groups for instructional purpose (5) When distributing literature and presenting visual material

Another part of this study was to try to determine the kind of literature and posters that had been found most effective in teaching patients. These materials were classified as (1) commercial, (2) those prepared by an organization staff for its own use and (3) those obtained from other noncommercial sources such as the United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Local and State Nutrition Associations, State Health Departments and so forth. Because information given on many of the questionnaires was not specific, evaluation of these data was not possible.

Interpretation of Data Returns on Questionnaire

The results from the mailing list described above were gratifying and probably indicated the growing interest in the subject. As shown in Table I, from a total of 452 forms mailed, replies were received from 251. This represents returns of 55.53 per cent. Six letters were returned unclaimed and 195 hospital administrators made no comment or did they return the questionnaire. Thirty-seven letters were received with miscellaneous statements such as explaining that the institution was closed or that they did not

TABLE I

Report of Questionnaire on Nutrition Education and Food Service in Tuberculosis Hospitals and Sanatoria in the U S as of August, 1947

RETURNS	Number	Per cent
TOTAL QUESTIONNAIRES SENT	452	100.0
TOTAL REPLIES	251	55.53
Questionnaires with adequate information	213	47.12
Questionnaires with inadequate information	1	0.22
Miscellaneous replies	37	8.19
UNCLAIMED MAIL	6	1.33
NO RESPONSE	195	43.14

now take tuberculosis patients Of the 214 questionnaires returned one had to be eliminated because it could not be classified for lack of information In the analysis of these data the facts presented are those submitted by 213 tuberculosis hospitals

Practices as They were Reported

Table II presents a summary of the 213 returned questionnaires Here we note that a small number of hospital staffs utilized the above mentioned opportunities for nutrition instruction, only 27.2 per cent took dietary histories upon admittance, 39.4 per cent kept dietary records during the period of hospitalization and 39.4 per cent provided special nutrition instruction to their patient population Of these sanatoria, a number concerned themselves only with those individuals who presented special dietary problems

Of the institutions that did try to carry on some type of program to instruct the patients those under Federal control were in the majority when checked on a percentage basis According to Table III, 75 per cent of this group reported that nutrition information was given either through individual conferences, group meetings, distribution of literature or combinations of these The County and City controlled hospitals were next with 40 per cent participating in such activities Among the 34 private hospitals questioned only 26.5 per cent indicated they had nutrition education programs

Among the methods used in teaching patients, individual conferences predominated Forty-six per cent of the hospitals under Federal control reported that they used this method while 10.7 per cent of them had group meetings, 14.3 per cent combined the group and individual conferences, and 3.6 per cent only distributed nutrition literature In institutions under other types of control less than 15 per cent reported that they gave nutrition information through individual conferences, while 13.3 per cent of County and City and 7.5 per cent of State hospitals provided group discussions A small number distributed various kinds of leaflets on the subject More than 60 per cent of the hospitals, with the exception of the United States government owned, gave no report which probably indicated that there was no attempt made to provide this type of instruction

Table II also reveals the extent to which the various kinds of materials were used Considering the combined reports of all hospitals it is obvious that in group three, literature prepared and distributed by the United States Department of Agriculture, State Health Departments and Nutrition Associations was used more frequently than the other two Again the institutions under Federal control differed from the others in that they used material pre-

pared by their own staff more often than that distributed by either commercial concerns or other official agencies

Among the users of visual aids, the Federal supported hospitals ranked the highest with 28.6 per cent of them utilizing the educational value of posters and charts and 21.4 per cent showing movies and slides on topics related to nutrition. Only 13.2 per cent of State owned and 10.2 per cent of County and City owned institu-

TABLE II

Summary of Information on Nutrition Education Obtained from 213 Tuberculosis Hospitals and Sanatoria in the U. S. as of August, 1947

TYPE OF CONTROL	DIETARY HISTORY UPON ADMITTANCE		DIETARY RECORDS DURING HOSPITALIZATION		NUTRITION EDUCATION (PATIENTS)	
	Number	Per cent	Number	Per cent	Number	Per cent
<i>Federal Control</i>						
Total	28	100.0	28	100.0	28	100.0
For all patients	3	10.7	4	14.3	15	53.6
For specials only	3	10.7	10	35.7	5	17.9
Not reported	22	78.6	14	50.0	8	28.5
<i>State Control</i>						
Total	53	100.0	53	100.0	53	100.0
For all patients	9	17.0	5	9.4	14	26.4
For specials only	3	5.7	16	30.2	2	3.8
Not reported	41	77.3	32	60.4	37	69.8
<i>County and City Control</i>						
Total	98	100.0	98	100.0	98	100.0
For all patients	17	17.4	10	10.2	30	30.6
For specials only	6	6.1	25	25.5	8	8.2
Not reported	75	76.5	63	64.3	60	61.2
<i>Private Control</i>						
Total	34	100.0	34	100.0	34	100.0
For all patients	15	44.1	6	17.7	8	23.5
For specials only	2	5.9	8	23.5	2	5.9
Not reported	17	50.0	20	58.8	24	70.6
<i>For All Types of Control</i>						
Total	213	100.0	213	100.0	213	100.0
For all patients	44	20.6	25	11.7	67	31.4
For specials only	14	6.6	59	27.7	17	8.0
Not reported	155	72.8	129	60.6	129	60.6

TABLE III
Summary of Methods and Materials Used in Nutrition Education Programs of 213 Tuberculosis Hospitals and Sanatoria in the United States as of August, 1947

	TOTAL		FEDERAL		STATE		COUNTY & CITY		PRIVATE	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
<i>How Presented</i>										
Total	213	100 0	28	100 0	53	100 0	98	100 0	34	100 0
Individual conferences	38	17 8	13	46 4	6	11 3	14	14 3	5	14 7
Group meetings	20	9 4	3	10 7	4	7 5	13	13 3	0	0
Combination of above two	15	7 1	4	14 3	3	5 7	5	5 1	3	8 8
Distribute literature only	12	5 6	1	3 6	3	5 7	7	7 1	1	3 0
No report	128	60 1	7	25 0	37	69 8	59	60 2	25	73 5
<i>Literature Used</i>										
Total	213	100 0	28	100 0	53	100 0	98	100 0	34	100 0
Commercial	11	5 2	4	14 3	1	1 9	6	6 1	0	0
Own	8	3 7	5	17 9	1	1 9	1	1 0	1	3 0
Others*	23	10 8	3	10 7	7	13 2	10	10 2	3	8 8
No report	171	80 3	16	57 1	44	83 0	81	82 7	30	88 2
<i>Visual Aids Used</i>										
Total	213	100 0	28	100 0	53	100 0	98	100 0	34	100 0
Slides and movies	11	5 2	6	21 4	2	3 8	3	3 1	0	0
Posters and charts	27	12 7	8	28 6	7	13 2	10	10 2	2	5 9
Food models	9	4 2	2	7 1	3	5 7	4	4 1	0	0
No report	166	77 9	12	42 9	41	77 3	81	82 6	32	94 1

*USDA, BHNHE, State Health Departments, etc

tions made use of posters and charts and approximately 3 per cent of them provided nutrition information by means of movies and slides. A small number of sanatoria used food models of some kind but these were primarily for teaching special diets. Of the 213 tuberculosis hospitals returning questionnaires 171 or 80.3 per cent made no report of literature used and 166 or 77.9 per cent did not comment on the type of visual aids used.

Comments

The information on nutrition education practices obtained through questionnaires sent to hospitals that care for tuberculous patients appears to substantiate the impression gained through interviews with patients as stated in the introduction. Few institutions of this kind have made specific plans to assist the patient to appreciate the part that food plays in treating the disease or in maintaining a healthy body. Of the various types of hospitals studied, those under Federal control apparently have done more towards utilizing opportunities and setting up nutrition education programs than have the others. There has been no attempt made to determine the reason for the practices reported other than to assume that hospitals under Federal control have larger staffs to carry on the program.

A gratifying part of this study was the observation that such a large number of administrators recognized the importance of these activities. Some requested materials and suggestions for initiating nutrition education programs while others said they were planning to start such programs within the next year. There were also many requests for tabulated results of the study.

SUMMARY

A two page questionnaire was sent to 452 tuberculosis hospitals and sanatoria in the United States in order to secure information as to the prevalence of nutrition education programs for patients.

Returns were received from 55.53 per cent of the hospitals of which there were 213 completely filled questionnaires which were used in evaluating nutrition activities.

Of these 213 hospitals approximately one third utilized available opportunities for presenting nutrition information to patients, with only 27.2 per cent taking dietary histories upon admittance, 39.4 per cent keeping dietary records during hospitalization and 39.4 per cent providing organized nutrition instruction.

The individual conference method of teaching was reported as being the most commonly employed by all hospitals. Visual aids appeared not to be in popular use.

Nutrition materials prepared and distributed by such agencies

as the United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, State Health Departments and State and Local Nutrition Associations appeared to have preference over all others

Interest in nutrition education for tuberculous patients was evidenced by comments made by administrators and the numerous requests for assistance in initiating such programs and securing materials. Many also were desirous of seeing the results obtained from the questionnaires.

Much of the information obtained in the study has not been incorporated in this article but will probably be presented in other papers at later dates.

CONCLUSION

Nutrition education for tuberculosis patients in hospitals located in all parts of the United States has apparently been neglected according to a study of practices reported by 213 tuberculosis hospitals and sanatoria. Increasing interest in this phase of the program for the care of tuberculous patients is evident. Those employed in the nutrition field might do well to become acquainted with the needs and activities in their particular communities and offer assistance to such institutions.

Acknowledgment The authors acknowledge with gratitude the cooperation of the hospital administrators in filling out the questionnaires and furnishing valuable information for the study and the assistance given by fellow staff members who so ably prepared and handled the questionnaires, tabulated the data and criticized the paper.

RESUMEN

Se envió un cuestionario que consistía de dos páginas a 452 hospitales y sanatorios para tuberculosos en los Estados Unidos, a fin de obtener datos acerca de la existencia de programas educativos para los pacientes sobre el asunto de la alimentación.

Se recibieron respuestas del 55.53 por ciento de los hospitales, entre las cuales hubo 213 cuestionarios llenados por completo, y estos son los que se emplearon en avaluar las actividades de alimentación.

De estos 213 hospitales la tercera parte, aproximadamente, utilizaron las oportunidades disponibles para presentar a los pacientes información sobre la nutrición, pero sólo el 27.2 por ciento tomaron historias sobre la dieta al tiempo de la admisión, el 39.4 por ciento llevaron datos sobre la dieta durante la hospitalización y el 39.4 por ciento proporcionaron una instrucción organizada sobre la alimentación.

La conferencia individual fue el método de enseñanza que más

generalmente usaron los hospitales. Aparentemente no fue comun el empleo de las ayudas visuales.

Los folletos sobre la alimentación preparados y distribuidos por agencias tales como la Oficina de la Nutrición Humana y la Economía Doméstica del Departamento de Agricultura de los Estados Unidos y las Asociaciones de Nutrición Locales y de los Estados, parecieron ser preferidos a todos los otros.

El interés en la educación de los tuberculosos sobre la nutrición fue manifestado por los comentarios que hicieron muchos de los administradores y por las numerosas solicitudes de ayuda para iniciar tales programas y para obtener materiales. Muchos también manifestaron deseos de saber los resultados obtenidos por los cuestionarios.

No se ha incluido en este informe mucha de la información obtenida en el estudio, pero probablemente se la presentara mas tarde en otros trabajos.

CONCLUSION

Aparentemente se ha descuidado la educación de los tuberculosos sobre la alimentación en hospitales situados en todas partes de los Estados Unidos, a juzgar por un estudio en el que participaron 213 sanatorios y hospitales para tuberculosos. Es evidente que existe un interés creciente en esta fase del programa de tratamiento de los tuberculosos. Aquellos que están dedicados al campo de la nutrición deberían enterarse de las necesidades y las actividades de sus respectivas colectividades y deberían ofrecer su ayuda a esas instituciones.

Sterile Hemopneumothorax Caused by Softening and Perforation of a Pulmonary Infarct

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Softening of a pulmonary infarct with perforation into the pleural cavity and formation of a sterile hemopneumothorax is unusual. A case demonstrating these events is given in this report. The usual course following pulmonary infarction is organization of the infarct and healing by fibrous scar formation. In some cases a hemorrhagic pleural effusion may develop.

The clinical diagnosis of hemopneumothorax resulting from the breakdown of a bland pulmonary infarct may be exceedingly difficult, especially in the absence of subsequent anatomical studies. No case of this type was encountered in ten years at the Mt Sinai Hospital of New York City by Berliner,¹ who in 1941 reviewed one hundred and twenty cases of hemorrhagic pleural effusion, ten of which were due to pulmonary embolization. Even the finding of a spontaneous hemopneumothorax is an infrequent finding. Berliner¹ encountered only six cases in a ten year period. Of these, one was due to pulmonary tuberculosis, one was proved to be due to a ruptured bleb, and the others were presumed to have the same cause. Helwig and Schmidt² in 1947 reported fourteen fatal cases of spontaneous hemopneumothorax which came to autopsy, but these were all due to ruptured blebs, or torn adhesions, or were of undetermined cause. Similar etiologies have been described in other publications.^{5,9}

Rawson and Cocke³ reviewed the literature in 1947, and found only five cases of perforation of a necrotic pulmonary infarct resulting in hemopneumothorax, they added a sixth case of their own. These cases were diagnosed at necropsy. We regard it worthwhile to report this, the seventh case, because the diagnosis was made during life, conservative treatment proved unavailing, and the clinical impression was confirmed by the necropsy findings.

CASE REPORT

A thirty year old, white male truck driver was admitted to the Salt Lake Veterans Administration Hospital for the third time on December 11, 1947, complaining of severe shortness of breath of two weeks' dura-

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tion He had been well until four years before entry, when he noted dyspnea, palpitation on exertion, intermittent cough, occasional hemoptyses and orthopnea A heart murmur was discovered two years prior to entry, although there was no history of rheumatic fever His first admission to this hospital, thirteen months before the present one, was necessitated by the increasing severity of his symptoms, he was found to have typical evidence of rheumatic heart disease, with mitral stenosis and insufficiency, cardiac enlargement, normal sinus rhythm, and mild decompensation Rapid improvement followed digitalization He returned for the second time two months prior to his final admission with a recurrence of his symptoms plus ankle edema The findings were similar to those found on his first admission The cardiac rhythm was regular, there was no fever and repeated blood cultures were negative Improvement after medical treatment again allowed him to return to work

Two weeks before the final entry, a sudden transient attack of dysarthria and paralysis of the left extremities occurred He noticed no fever, petechiae, nor irregularity of the heart Five days prior to admission a dull aching pain appeared in the right chest posteriorly, radiating around to the front, which was made worse with coughing The sputum was tinged with blood Nausea, vomiting, diarrhea and indigestion also occurred, followed by increasing dyspnea, swelling of the ankles, and a yellowish discoloration of the skin

Physical examination showed an acutely ill, slightly jaundiced, dyspneic and orthopneic young white male T 100 degrees F, P 96, R 30, and B.P 125/80 There was an increase in the A-P diameter of the chest with a slight bulging of the precordial region A respiratory lag was observed on the right Tactile fremitus was diminished over the right lung On percussion there was flatness over the right chest posteriorly, below the level of T-10, with hyperresonance above Auscultation showed



FIGURE 1



FIGURE 2

Fig 1 Chest plate taken during patient's second admission It reveals a mitral configuration of the heart—Fig 2 Chest film taken on the last admission Right sided pneumothorax with fluid to the level of the third rib anteriorly There is also obliteration of the left costophrenic angle

diminished breath sounds on the right, and coarse rales on the left. A presystolic thrill was felt at the cardiac apex. The area of cardiac dullness was enlarged, the point of maximal impulse was just outside the midclavicular line in the sixth interspace. At the apex a loud, blowing systolic and a low pitched presystolic murmur were heard. The rhythm was regular. P2 was equal to A2. The liver edge was felt four finger breadths below the right costal margin, and there was three plus pitting edema over the lower legs and ankles.

Laboratory work The urine on admission contained 1 plus albumin and bile while the sediment was normal. Hgb 17 Gm, Ht 51, WBC 18,500 with 80 per cent polymorphonuclear neutrophilic leucocytes, 20 per cent lymphocytes, blood Kahn negative, BUN 11 mg per cent, prothrombin content 61 per cent, thymol turbidity 4 units, direct bilirubin 0.5 mg per cent, indirect bilirubin 1.7 mg per cent. On admission the two hour urine urobilinogen was 4.4 units, rose to 10.8 units three days later, and returned to normal only after several weeks.

Roentgenograms Films taken on admission (Fig 2) showed the right lung to be partially collapsed, and there was a large amount of fluid and air in the right pleural space, with shift of the mediastinum to the left. The left costophrenic angle was obliterated. The heart appeared enlarged. Repeat roentgenogram of the chest on the third hospital day following thoracentesis showed a decrease in the amount of fluid in the pleural space (Fig 3). A definite disease process in the right lower lobe could be distinguished on the film on the seventeenth hospital day after catheter drainage (Fig 4).

Repeated electrocardiograms were all normal except for large P waves in Leads I and II. At no time were changes discovered consistent with acute cor pulmonale despite the use of unipolar limb and chest leads in addition to the standard leads.

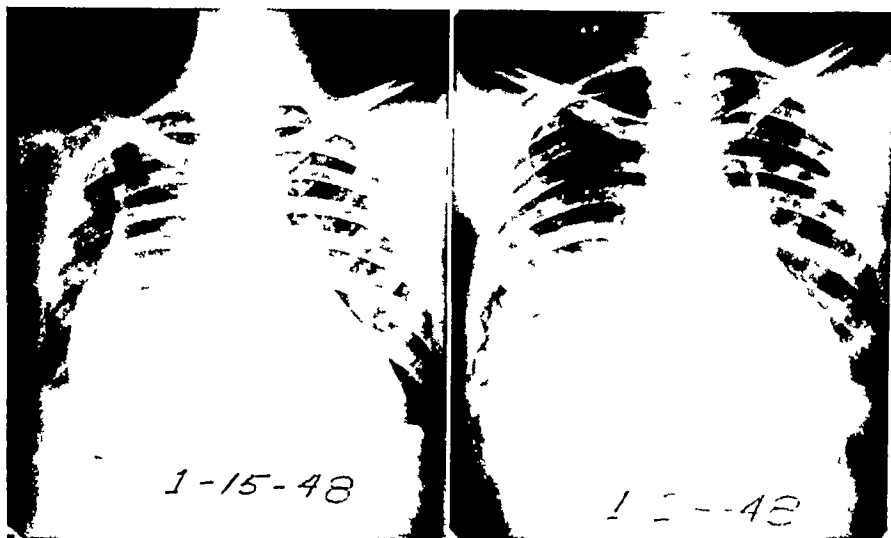


FIGURE 3

FIGURE 4

Fig 3 Chest x-ray film subsequent to the removal of 1400 cc of bloody fluid from the right pleural space—Fig 4 The presence of right lower lobe pathology is revealed following drainage of the right chest by an indwelling rubber catheter connected to a water trap

The course in the hospital was as follows. Full digitalization was accomplished. Right thoracentesis shortly after admission yielded 1400 cc of red amber fluid with a specific gravity of 1.010. Microscopic examination revealed 200,000 red blood cells per cubic mm, 5,000 white blood cells, mostly polymorphonuclear neutrophilic leucocytes. Culture was negative. No neoplastic cells were seen in a centrifuged specimen. Thoracentesis was performed again on the fourth hospital day and 600 cc of red fluid was removed. This had a specific gravity of 1.012. It was loaded with red blood cells and some white blood cells, the majority of which were polymorphonuclear neutrophilic leukocytes. Culture was again negative. Penicillin in water (200,000 units) was introduced into the pleural cavity. By intramuscular route, 500,000 units of penicillin were given every eight hours. The prothrombin content was maintained between 20 and 50 per cent of normal by means of dicoumarol. On the eleventh hospital day, a soft rubber catheter was inserted into the right chest, connected to a water trap and reddish fluid and air under pressure were evacuated. One hundred thousand units of penicillin were instilled into the catheter every other day. Ten days after its insertion, the catheter was clamped off, but the patient promptly developed respiratory distress. A chest film showed further collapse of the right lung (Fig. 5). The catheter was then unclamped and a large amount of air poured out. The patient was placed on a salt-free diet. In addition he received ammonium chloride, mercurhydrin intramuscularly and intravenously, and calcium theobromine salicylate by mouth, all without marked effect on his edema. On January 31, 1948 (25th hospital day), he had an episode of confusion with auditory and visual hallucinations. The patient was placed on six grams of acetylsalicylic acid daily without improvement. He continued to have severe hallucinatory episodes and became increasingly dyspneic and cyanotic. His pulse rate was never slower than 90, although intake of digitoxin was pushed to 0.4 mg daily. On February 21, 1948 all medication except penicillin and 0.1 mg digitoxin was discontinued. On February 22, 1948 the patient was placed in an oxygen tent because he became too psychotic to utilize an oxygen mask properly. His pulse remained at 100 and was regular in rhythm. His respirations became slow and labored. He became very cyanotic and semi-comatose and quietly expired on the 47th hospital day.

At necropsy (Courtesy Dr. Frank R. Ellis), which was limited to the thorax, the right lung was atelectatic, and the right pleural cavity was filled with air and 50 cc of brown fluid. Examination of the right lung showed emboli occluding the right superior pulmonary artery, secondary branches of the middle pulmonary artery, and a large branch of the inferior pulmonary artery. In the lower lobe, there was a large infarct measuring 3 x 4.5 x 5 cm, in the center of which was a perforation 1.5 cm in diameter extending 1 cm into the parenchyma and communicating freely with the pleural space. An infarct was also present in the upper lobe. The left lung also contained large infarcts peripheral to emboli in the main branches of the arteries to the left upper and lower lobes (Fig. 6). Microscopic examination revealed multiple hemorrhagic infarcts, some showing liquefaction necrosis with large foci of neutrophilic infiltration. One infarcted area revealed many large fusospirochetal rods. These organisms did not grow on cultures obtained at postmortem. There was obliteration of the left pleural cavity by fibrous adhesions, except for two loculated spaces containing brown fluid at the left base.

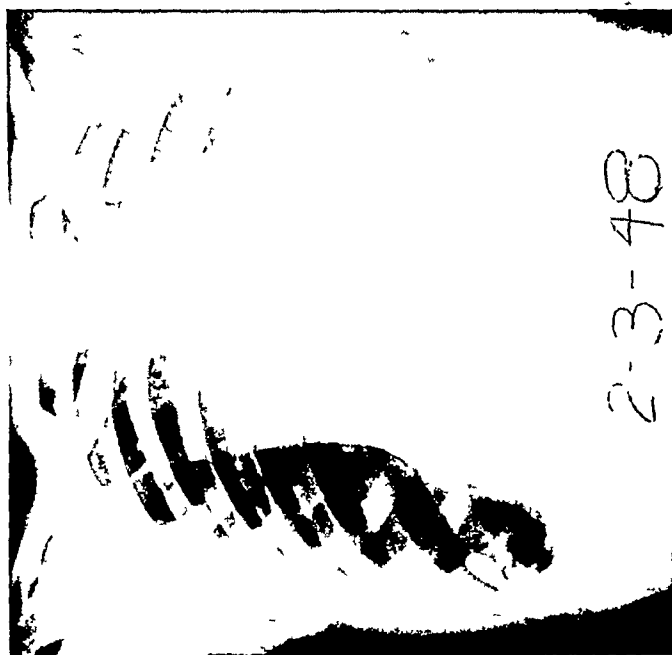


FIGURE 5

Fig 5 This roentgenogram reveals the rapid development of a tension pneumothorax within several hours after the catheter was clamped off —*Fig 6* The pathologic specimen shows multiple pulmonary emboli with subsequent infarction The arrow indicates the site of the ruptured infarct The circles show sites of emboli



FIGURE 6

Examination of the heart revealed cardiac enlargement, mitral stenosis with calcified nodular valvulitis, and a small mural thrombus in the right ventricle. There was extensive fibrosis of the myocardium of the right ventricular wall and moderate atrophy and fibrosis of the left ventricular wall. Evidence of active rheumatic changes were not present.

Comments

The antemortem diagnosis of a ruptured pulmonary infarct was made possible by the unusual combination of jaundice and hemopneumothorax. Jaundice has not been reported as a sequel of hemopneumothorax due to the usual causes while icterus as the result of infarction is not at all uncommon. Failure of the pleuro-pulmonary communication to heal during a period of forty-seven days despite closed drainage mitigated against simple rupture of a bleb or dissection by mediastinal air and favored the presence of a necrotic non-healing area between lung and pleura. In addition, the patient's cardiac decompensation and inactivity certainly predisposed to the formation of thrombi with embolization. The sudden onset of chest pain probably followed an episode of embolization.

Waring⁴ includes hemorrhagic pleural effusion under the heading of hemothorax. In this case, pure blood may have been present in the pleural cavity initially, only to be diluted with serous fluid caused by irritation,¹ or effusion due to the decompensation may already have been present when the bleeding took place. Thus, we believe there is justification in the use of the term hemopneumothorax in this case. The fluid was sterile on admission, as shown by the negative cultures, but may have become infected during the long continued catheter drainage. The complete ineffectiveness of apparently adequate dicoumarol therapy in preventing multiple embolization is of interest, as are the failure of the perforation in the right lung to close and the poor response to intensive treatment of the cardiac decompensation. The source of the emboli remains open to question, they may have come from mural thrombi in the heart, but more likely originated in the veins of the legs.

SUMMARY

A case of chronic rheumatic heart disease with decompensation is reported, in which embolization and pulmonary infarction were followed by softening of an infarct, perforation into the pleural cavity, and sterile hemopneumothorax.

RESUMEN

Se informa sobre un caso de enfermedad reumática crónica del corazón con insuficiencia, en el que embolias e infartos pulmo-

nares resultaron en reblandecimiento de un infarto, perforación en el espacio pleural y hemoneumotórax estéril

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Spontaneous Perforation of the Normal Esophagus

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Spontaneous perforation of the esophagus is a distinct clinical entity, in which, sudden rupture through all layers occurs in the lower end of a normal esophagus. Such a perforation of the esophagus occurs usually after violent retching or vomiting. Acid gastric contents and food particles are driven into the mediastinum, left pleural cavity and also occasionally the right pleural cavity. The resulting insult in this unique esophageal lesion is devastating to the patient. The features of the disease are distinctive yet easily missed; thus the diagnosis has been rarely made during life so that definitive treatment could be instituted.

Perforations of the esophagus complicating endoscopy or due to carcinoma, stricture or other pre-existing pathological conditions are not considered in this discussion. The diagnosis of perforation of the esophagus after endoscopy or dilatation, for example, is relatively easy. Similarly, if the esophagus is the site of a known pathological process, there is little or no diagnostic problem, and treatment may be instituted at once. Perforations due to these conditions are usually less fulminating in character than the lesion under discussion. An empyema or mediastinitis may develop over a period of time and with adequate drainage, chemotherapy and supportive treatment, the patient has a good chance of recovery.

There are several disease syndromes recorded in the literature which are closely related to spontaneous perforation of the esophagus. The lesions in these syndromes are produced by the same fundamental forceful and/or disarranged vomiting mechanism. However, the patient's subsequent clinical course varies and is conditioned by the degree and extent of the resultant esophageal laceration and the possibility of its superimposition on an esophagus already the site of disease.

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A) *Hyperemesis Gravidarum*

The severe itching and vomiting characteristic of this disease syndrome is well known. Acute longitudinal tears in the mucosa at the lower end of the esophagus may result in severe or fatal hematemesis.

B) *Mallory Weiss Syndrome*

This syndrome presents fatal hematemesis in an alcoholic following a prolonged debauch with vomiting and retching. The lesion is a longitudinal tear in mucosa or muscularis, usually at the cardia of the stomach and the lower end of the esophagus. Such a laceration in a cirrhotic patient with portal hypertension and esophageal varices may understandably be rapidly fatal from acute blood loss.

C) *True Spontaneous Esophageal Perforation*

The esophagus is lacerated through all layers, in a longitudinal direction, by vomiting. Gastric juice and food particles are propelled into the mediastinum with consequent gross contamination of it and frequently one or both pleural cavities. In addition air may collect in the mediastinum or pleural cavities under tension and hasten the fatal outcome. This disease entity is the most inexorably ruthless of all esophageal perforations and understandably has carried a one hundred per cent fatal prognosis until very recent times.

We wish to review briefly the clinical aspects of these patients, stress the diagnostic features, mention our laboratory experiments, report a case correctly diagnosed but unsuccessfully treated by surgical means and offer our considered views on the proper surgical and supportive treatment necessary in an attempt to save these patients.

Historical Aspects

In 1724 Boerhaave's classical description of the first case of spontaneous perforation of the esophagus, occurring in the Grand Admiral of Holland, Baion DeWassenaer, was recorded. This has been quoted by Barrett.¹ Fitz² in 1877 made the first review in the American literature and recorded a case. In 1914, in a review, Walker³ found 22 cases including his own, which was the first case diagnosed during life. Other comprehensive reviews include Smead,⁴ 1931, Ridgeway and Duncan⁵ in 1937, and Klein and Grossman⁶ in 1943, who uncovered only 40 cases. Recent reports are those of Collis,⁷ 1944, Barrett,¹ 1946, and Eliason and Welty,⁸ 1946.

In one of the cases reported by Eliason and Welty⁸ the diagnosis was made during life. This represents the fifth time to our knowledge that the correct diagnosis has been made antemortem in this condition. Unfortunately no definitive treatment could be given this patient. Barlett¹ reports three cases in one of which the correct diagnosis was made, but no surgical treatment could be instituted. Collis⁷ patient was a healthy 45-year-old soldier on whom a thoracotomy was performed, the esophageal rent closed and the pleural cavity drained, but despite this definitive treatment, the patient succumbed ten hours later.

Recently Barlett⁹ has reported the first case known to us of survival of a spontaneous perforation of the esophagus. His patient had a subtotal hysterectomy then vomited violently 13 days postoperatively. Diagnosis was made by thoracentesis and roentgen examination and operation performed ten hours later. The esophageal perforation was closed by a purse-string suture and the chest drained. The immediate course was good. Three weeks later, a mediastinal abscess required drainage. Two months later, an abscess of the right upper lobe was noted, however, this drained spontaneously and the patient was well thereafter. Our colleague, Doctor Joseph P. Lynch,¹⁰ has likewise successfully treated a classical case recently by early operation and suture of the esophageal perforation, as outlined in this study. This case will be reported in detail at a later date by him.

Etiology and Pathogenesis

In spontaneous perforation, the stage is usually well set by a fairly standard set of circumstances. The patient usually has a full stomach at the time he retches violently, gastric contents are ejected exerting great expansile pressure on the upper gastric and lower esophageal wall, with resultant rupture of the distal esophagus. If the esophagus is obstructed even transiently by a bolus of undigested food leading the column of vomitus, the possible mechanism becomes even more apparent.

Rupture occurs in the lower end of the esophagus apparently due to an inherent weakness of this anatomic area. MacKenzie, quoted by Smead,⁴ removed the esophagus from 18 specimens at postmortem examination and ruptured them by water pressure. In 17 cases, the tear occurred in the lower third of the esophagus with from 5 to 11 pounds pressure.

A congenital and anatomic weakness of the lower end of the esophagus has been postulated by Menne and Moore¹¹ on the basis of their case of spontaneous esophageal perforation in a five-month-old infant following repeated vomiting spells. A curd stuck in the infant's esophagus and throat. The baby vomited

once more following this and died of a typical ruptured esophagus thirty-six hours later. They state that there are three other authentic cases in the literature over a 200-year period occurring in infants and children.

There is a strong alcoholic history in many of these patients. Ridgeway and Duncan⁵ reported 18 of 35 cases as having a significant alcoholic history, 7 cases denied indulgence and 10 cases were questionable or not stated. They felt, therefore, that regurgitation of gastric juice with digestion and/or acute ulceration might very well be a confusing etiological factor and make it difficult to evaluate microscopic changes in the esophagus as to their occurrence before or after rupture.

Alcohol may be an important factor in other ways. Excessive amounts often produce retching and vomiting and also tend to produce incoordinated muscle action that may impair critically the complicated vomiting mechanism.

Gluttony may be a factor since the full stomach is perhaps more easily compressed between the diaphragm and abdominal wall.

According to Weiss¹² vomiting is a complex reflex act composed of a number of highly coordinated bodily changes that he describes as follows:

- (1) During the stage of nausea, the pylorus closes and the cardia and esophagus dilate.
- (2) Reverse peristalsis carries gastric contents to the cardia and esophagus.
- (3) At the onset of retching, the diaphragm descends to the position of deep inspiration.
- (4) Gastric contents are then ejected with great force by this sudden convulsive increase of intrathoracic and intra-abdominal pressure.
- (5) Repeated attacks of vomiting at short intervals, however, may fatigue the vomiting center with consequent loss of coordination.
- (6) Gastric contents may then thrust with even greater force against the cardia and lower esophagus if relaxation of the esophagus and descent of the diaphragm do not occur at a properly timed juncture with the forceful retching movement.

Pathology

- 1) Postmortem examination of a patient who has died as a result of spontaneous perforation of the esophagus reveals a remarkably constant and characteristic lesion. The rupture almost invariably occurs in the lower one-fifth of the esophagus, in a longitudinal direction and on the left posterolateral aspect. The tear is usually sharp edged and incised in appearance. It may be several centimeters in length but may be small and difficult to demonstrate. Rarely the rupture has been reported as occurring transversely, on the right, high in the esophagus, or below the diaphragm. The appearance in microscopic sections varies with

the survival time of the patient and the interval between death and postmortem examination. The majority of pathologists seem agreed that rupture occurs in the "true" case in a normal esophagus, that there is no evidence of pre-existing disease, and that all tissue changes are due to the severe chemical and bacterial inflammation.

2) There are, immediately, several possible mechanisms resultant upon a spontaneous rupture of the esophagus: (a) Rupture into the mediastinum and left pleural cavity which is the commonest lesion; (b) Rupture into the mediastinum and both right and left pleural cavities; (c) Rupture into the mediastinum and right pleural cavity only; (d) Rupture into the mediastinum alone or with later perforation into either pleural cavity; (e) Direct rupture into the mediastinum and/or pleural cavity. A devastating, necrotizing chemical insult with rapidly superimposed aerobic and anaerobic infection quickly jeopardizes the patient's life and he succumbs to the gangrenous mediastinitis, pleuritis, pyopneumothorax, and emphysema usually in a matter of several hours to 1 or 2 days. The pyopneumothorax may exhibit signs of tension, varying degrees of atelectasis are present, and mediastinal emphysema may cause thoracic inlet obstruction. The latter impairs inflow to the right heart with consequent peripheral vascular collapse and profound shock. Varying amounts of fluid and gastric juice, often bloody, together with partially digested food particles will be found in the mediastinum and/or pleural cavities. A pericardial effusion may ensue if the patient survives for any length of time.

Symptoms and Signs

The catastrophe of spontaneous esophageal perforation is usually seen in a male between 35 and 55 years who had a history of heavy or excessive alcoholic intake. Finally, one of these indulgences is accompanied by severe retching or vomiting and at this time rupture of the esophagus is particularly apt to occur.

In Walker's³ series of collected cases, 20 of 22 patients were males. Only 5 of the 35 cases reported by Ridgeway and Duncan⁵ were females. According to Menne and Moore¹¹ 3 authentic cases have been reported in children in addition to their case.

Vinson¹³ has reported several cases in which pernicious vomiting of pregnancy caused acute lacerations in the lower end of the esophagus later resulting in a stricture if the patient survived. These cases are undoubtedly counterparts of the cases reported by Mallory-Weiss.¹⁴ In the Mallory-Weiss syndrome, vomiting and retching occurs in chronic alcoholics during a prolonged debauch leading to hematemesis from a long tear through the mucosa or

even into muscularis of the lower esophagus or gastric cardia. Indeed, one of the patients reported by Mallory and Weiss was a hyperemesis gravidarum case with an identical lesion to that observed in alcoholics. The cases of Vinson and Weiss and Mallory may be regarded as incomplete ruptures of the esophagus.

Cases have also been reported as occurring during a convulsive seizure, defecation, seasickness and retching during or following recovery from general anesthesia.

In most instances, the onset of symptoms is sudden, and the patient rapidly becomes acutely and seriously ill. Usually after vomiting or retching, the patient is suddenly seized with violent pain and may volunteer that he feels as though something was "torn inside."

Pain is continuous and excruciating, and may be felt low in the chest, over the xiphoid, may radiate through to the back, or may be referred to the shoulder or upper abdomen. Morphine or demerol even in huge doses do not alleviate the patient's discomfort.

Shock is invariably present. The patient is anxious and apprehensive. He may be restless or may remain immobile with trunk flexed. There may be slight cyanosis and the respirations are usually rapid, shallow and grunting. The skin is cold and clammy, the blood pressure low, the temperature normal or sub-normal and the pulse fast and thready.

Thirst is insatiable, although pain may be intensified as swallowed fluid passes into the mediastinal and pleural spaces.

Upper abdominal spasm and tenderness may be prominent before the chest findings are manifest. Exploratory laparotomy has been performed frequently in the past for this reason.

The Chest findings include signs of fluid relatively early. Later, atelectasis and pyopneumothorax are present. The pneumothorax may manifest signs of tension by dyspnea, cyanosis and displacement of the mediastinum to the opposite side.

Subcutaneous Emphysema is a very important and helpful sign and should lead one to the diagnosis if present. Usually, it is present in two-thirds of the cases, appearing first in the supra-sternal notch and supraclavicular fossae, and later spreading so as to involve the face, trunk or even the extremities and dissecting widely in the subcutaneous tissue.

Thoracentesis will clinch the diagnosis in the suspected case. Varying amounts of air may be aspirable. The fluid present usually is sour and in appearance often seems tinged by old changed blood, presumably due to the action of gastric ferments. A thin serous fluid may be present in either pleural cavity if

the infection is confined to the mediastinum. A few hours later this fluid likewise will be invaded by organisms.

Roentgenography may be extremely helpful and is important in the differential diagnosis and as a possible means of early diagnosis. The roentgenogram may confirm the signs of fluid in one or both pleural cavities, demonstrate atelectasis or pneumothorax and corroborate mediastinal displacement. Emphysema may be detected in the root of the neck or in the mediastinum. If rupture has occurred only into the mediastinum, a fluid level may be demonstrated. The absence of air under the diaphragm is helpful if there is doubt as to the location of the primary lesion.

Many of the classic findings in perforated esophagus may be evident only shortly before the patient succumbs. However, if the diagnosis is suspected, thoracentesis and suitable roentgenograms will often solve a perplexing differential problem long before emphysema appears. The difficulty now is not really in making the diagnosis but rather in making it early enough to have definitive surgery offer some chance to the afflicted individual.

Differential Diagnosis must include (1) acute coronary thrombosis, (2) perforated peptic ulcer, (3) acute pancreatitis, (4) dissecting aneurysm of the aorta, (5) acute cholecystitis, (6) spontaneous pneumothorax, (7) pulmonary embolism, (8) mesenteric occlusion, (9) interstitial emphysema, (10) diaphragmatic hernia.

Laboratory Experiments

Following the unsuccessful case herein reported the production in the laboratory of a lesion exactly comparable to a spontaneously ruptured esophagus was attempted. The creation of an esophageal defect by various methods through the esophagoscope was unsatisfactory because a truly comparable lesion could not be produced and no two perforations by such methods were alike, the mediastinum was not widely opened nor even necessarily contaminated and the right pleural cavity was not opened. Such procedures were, therefore, abandoned.

Eventually, in order to produce a standard defect analogous to the human case, a thoracotomy was done and the lesion produced under direct vision in spite of the obvious disadvantages of assessing therapy on an animal who has had a previous thoracotomy. A standard procedure was used in each animal. The animal was fed then anesthetized with intravenous nembutal, shaved and prepped, an endotracheal tube inserted, and the animal placed in the right lateral decubitus position. The chest was opened through a left intercostal incision in the seventh interspace. The esophagus was mobilized up to the arch and the right and left pleural cavities and mediastinum widely opened. A two-inch left

postero-lateral incision through all esophageal layers was then made approximately $1\frac{1}{2}$ inches above the esophageal hiatus Ten milligrams of apomorphine was given then intravenously supplemented by manual compression of the animal's full stomach Large amounts of gastric juice and previously eaten food were regurgitated with great force into the mediastinum and both pleural cavities The lungs were expanded under positive pressure, air was aspirated from the right and left pleural cavities while the chest wall was closed in layers A drainage tube was led out to an underwater seal In this fashion, a lesion was produced analogous to the human case in its most severe form, namely, with both pleural cavities, as well as the mediastinum, widely involved by gastric juice and food particles

The animals were divided into three groups (a) completely untreated, (b) supportive treatment by parenteral fluids, sulfadiazine and penicillin, (c) operative closure of the esophagus at varying intervals and pleural drainage with parenteral fluids, penicillin and sulfadiazine

GROUP I—UNTREATED

Animal	Survival	Post Mortem Findings
Dog No 1	40 hours	Putrid empyema and mediastinitis
Dog No 2	1 hour	Mediastinal emphysema Pneumothorax
Dog No 3	18 hours	Putrid empyema and mediastinitis
Dog No 4	Less than 1 hour	Mediastinal emphysema Tension pneumothorax
Dog No 5 (unfed)	Survived	
Dog No 5 (fed)	7 hours	Previous esophageal lesion firm fibrous tissue repair Many adhesions Recent esophageal laceration Empyema and mediastinitis

These animals were intended to serve mainly as a control group An attempt was made to restore their cardio-respiratory physiology to normal as the chest was closed, but no further treatment was given As might be expected, varying degrees of pneumothorax and mediastinal emphysema resulted Varying amounts of sero-sanguinous fluid was found in the pleural cavities This fluid invariably became thicker and more foul the longer the animal survived In Dog No 5 (unfed) there was no gross contamination by food or gastric juice The edges of the esophageal lesion bled

freely and there was a large clot in the left pleural cavity as the chest was closed. Persistent leakage was prevented probably by this fact. In any event, the animal survived and 3 months later, the chest was re-opened. The site of previous laceration was firmly repaired but the scar was apparent on careful palpation. There were numerous adhesions, however, and the examination was otherwise not remarkable. This case presumably illustrates the importance of the gastric juice and resultant chemical pleuritis as a factor of this lesion, particularly in view of the low PH values of the dog's gastric juice. When this animal's esophagus was again lacerated, this time on a full stomach, death occurred in the usual fashion 7 hours later.

GROUP II—SUPPORTIVE TREATMENT

Animal	Survival	Post Mortem Findings
Dog No 6	18 hours	Putrid empyema, mediastinitis, minimal mediastinal emphysema, partial atelectasis, left lower lobe
Dog No 7	18 hours	
Dog No 8	18 hours	

These animals all received 400-800 cc of 10 per cent glucose in saline intravenously according to their weight. Two hundred thousand units of penicillin were placed in the chest before closure. Sodium sulfadiazine (1 grain per pound) was mixed in the intravenous fluids at the conclusion of operation. Penicillin was then given in a dose of 100,000 units intramuscularly every eight hours and sodium sulfadiazine (1 grain per pound per 24 hours) was given subcutaneously every eight hours. The intravenous fluids were repeated 12 hours following operation. Post-mortem examination revealed the findings charted above.

Group III Operative and Supportive Treatment

A thoracotomy was performed and the usual esophageal laceration produced. Eight hours after perforation (to allow for diagnosis in the human case) fluids, sulfadiazine and penicillin were begun. Animals Nos 9, 10, 11, and 12 were then re-operated upon at intervals after perforation of 16, 11, 8 and 8 hours respectively, and the perforation closed. In all these animals, the chest was re-opened by subperiosteally resecting the left ninth rib. The pleural cavities were thoroughly irrigated. The esophageal rent was closed by an inverting Connell suture of 1-0 chromic catgut. The muscular layer was closed by multiple interrupted Lembert sutures of 3-0 silk. A drainage tube was led out through the tenth interspace and connected to an underwater seal. The

chest wall was closed in layers Supportive therapy was then continued by the same schedule outlined for Group II These animals died, 24, 15, 10, and 10 hours postoperatively, respectively In animal No 12 only the left pleural cavity was opened at the time of perforation of the esophagus with no apparent change in the end result

Animal No 13 This animal had his esophagus perforated Eight hours later supportive treatment was instituted and twenty-four hours later, he was re-operated and the esophageal lesion closed in two layers The animal did very well until the seventh post-operative day when he became distended and died a few hours later Postmortem examination revealed an essentially normal chest cavity with the esophagus well closed Abdominal examination revealed generalized peritonitis

Then in an attempt to evaluate the time element and the trauma of a previous thoracotomy, the esophagus in three additional animals was perforated The esophageal laceration was sutured immediately Two of these animals survived

Animal No 14 and animal No 16 The esophagus was perforated and the mediastinum and pleural cavities contaminated forcefully by vomitus, then thoroughly irrigated with saline which was aspirated The esophageal rent was closed at once in two layers Chemotherapy was stopped 24 hours later, and the chest drainage tube removed The subsequent course of these dogs was completely uneventful

Animal No 15 The esophagus was perforated in the usual manner and immediately sutured using the same technique as

GROUP III — SUPPORTIVE AND OPERATIVE TREATMENT
Esophageal Perforation Closed at Varying Intervals

Animal	Closure Esophageal Perforation		Survival	Post Mortem Findings
Dog No 9	16 hours	40 hours	} Esophagus well closed Pleural and mediastinal inflammation No suppuration	
Dog No 10	11 hours	26 hours		
Dog No 11	8 hours	18 hours		
Dog No 12	8 hours	18 hours		
Dog No 13	24 hours	7 days		Peritonitis
Dog No 14	Immediate	Survived		
Dog No 15	Immediate	24 hours		Putrid empyema and mediastinitis
Dog No 16	Immediate	Survived		
Dogs 9-13 inclusive had two thoracotomies				

in the other animals. In spite of the usual postoperative measures, the animal died twenty-four hours later. Postmortem examination revealed the esophagus to be well closed but putrid empyema and mediastinitis were present.

Comment

The severest possible form of esophageal perforation was produced with contamination of the widely opened mediastinal and pleural cavities. No absolute conclusions can be drawn from such a small series of dogs, however, the results are suggestive.

The group of animals with no treatment and with supportive care only show no great variation in time interval between perforation and the expected result. The animals, in whom the laceration was sutured at a subsequent operation, tended on the whole, to live a few hours longer and one of these animals, with a 24-hour interval between laceration and suture of the perforation, lived seven days and then did not die of chest complications. Three animals had their esophageal perforations closed immediately. The subsequent course of two of these animals was uneventful. The other animal, however, died of continuing mediastinal and pleural infection. The prolonged or complete survival of an animal with so severe a lesion seems to us directly related to the closure of the rent and the consequent prevention of continued contamination of the mediastinal and pleural cavities.

In view of the known disastrous course in the human patient with an untreated esophageal perforation and the uniformly fatal course in all dogs whose closure was delayed longer than the immediate termination of the acute experiment, it is difficult to explain the survival times of dogs nine to thirteen inclusive since these were in inverse relation to the interval between perforation and closure. The obvious explanation would seem to be the increased interval between the thoracotomies performed first to create the lesion and then to institute treatment in each animal. These animals surviving longest had the greatest time interval in which to recover from the primary thoracotomy. The animals in whom suture was immediately performed are more strictly comparable to human cases and to Groups I and II inasmuch as only one thoracotomy was performed. The essential difference is closure of the esophageal laceration in these comparable cases, with a change from 100 per cent mortality to 67 per cent survival. In this group of dogs, Nos. 9-16 inclusive, who were treated ideally with time intervals approximating the problem in the human, the survival rate was such (2 out of 8) that we believe that the results of the experiments suggest that the rationale of treatment is justified.

CASE REPORT

This 53-year-old laundry worker entered Boston City Hospital for the first time on May 7, 1946

Chief Complaint Excruciating epigastric pain for six hours

Present Illness Patient had never been seriously ill prior to this admission. At 6 30 P M on May 7, he ate lamb stew. The entire family became nauseated and the patient vomited mildly at 7 00 P M. He then attended a club meeting where he drank two bottles of beer. He returned home at 9 30 P M feeling ill, vomited repeatedly, and shortly experienced

(a) Severe, sharp, high epigastric and low left chest pain. The pain began anteriorly and radiated around to the back and also to the left shoulder.

(b) Sweating with a cold clammy feeling.

(c) Vomiting of clear gastric juice without blood.

At 1 30 A M the patient was seen in the emergency ward and given one-quarter of a grain of morphine sulfate on the admitting floor and sent to the ward with a probable diagnosis of acute coronary thrombosis.

Physical Examination Temperature, 98 degrees F, pulse, 140, respiration, 32, blood pressure, 130/90. Inspection revealed a very apprehensive, obese, middle aged male who was cyanotic, clammy, and in acute excruciating pain in spite of morphine. Respirations were rapid and painful. The patient was twisting and turning on the litter and complaining of thirst. His pupils were pinpoint. Chest examination was negative on percussion and auscultation except for high diaphragms. The heart not enlarged. Normal sinus rhythm at a rate of 140. The abdomen was boardlike with high epigastric tenderness. No peristalsis was heard. The reflexes were hyperactive.

Laboratory Data Hgb, 90 per cent, WBC, 20,800, Polys, 96, Lymphs, 4, Platelets and RBC, normal.

Hospital Course The patient continued to complain of thirst and of excruciating pain. He received one-half grain of morphine, one grain of codeine and one hundred milligrams of demerol in a period of two hours with no relief. The electrocardiogram was of no significance. The urinary diastase was normal. The flat and sitting abdominal roentgenograms revealed no fluid levels or air beneath the diaphragms. A general surgical consultant believed the abdomen was not a surgical problem. Chest roentgenograms revealed elevation of the left diaphragm and a hazy opacity at the left base. There was no fluid level. (Later review of this film revealed emphysema of the mediastinum.) The patient was maintained on nasal oxygen, demerol and penicillin. At 8 00 A M on May 8, the patient's blood pressure was 100/70 and the abdomen was rigid. Neck swelling with crepitation was present and air was beginning to dissect in the tissue planes of the face. A diagnosis of mediastinal and subcutaneous emphysema was made. A portable chest x-ray film revealed a partial collapse of the left lung, mediastinal shift to the right with fluid obscuring the left lung field, elevation of the left diaphragm and subcutaneous and mediastinal emphysema. The Thoracic Surgery Service was called in consultation and the patient seen by one of us (JWS) and a diagnosis of spontaneous perforation of the esophagus was made. A thoracentesis revealed fluid with food particles and low PH and the diagnosis was thus confirmed.

The patient's condition at this time was extremely precarious and it

was felt that he would tolerate little if any operative manipulation. A whole-blood transfusion was started then under local one per cent procaine infiltration a closed intercostal catheter drainage was performed in the seventh left interspace in the posterior axillary line on May 8 at 12 00 A M. A large amount of extremely foul thin cloudy fluid together with a large amount of air was immediately aspirated on opening the catheter to the underwater seal bottle. The patient was then transferred to the ward in poor condition. Intravenous fluids and blood were given. A positive pressure mask was used to deliver oxygen. Penicillin was given in doses of 30,000 units intramuscularly every two hours. Sodium sulfadiazine was given intravenously once then discontinued because of the poor urinary output. In spite of medication, the patient was obviously in severe pain, he was perspiring profusely, his color was only fair even with positive pressure oxygen. His pulse was weak and thready with a rate of 116 to 140, blood pressure remained at shock levels. Abdominal distention made it even more difficult for the patient to aerate properly. The patient was catheterized approximately 20 hours after admission, and fifty cubic centimeters of highly concentrated urine was obtained. His non protein nitrogen was 76, total protein, 6.56, carbon dioxide, 39 per cent, red blood count 4,000,000, and white blood count, 17,500. A right thoracentesis revealed forty cubic centimeters of cloudy serous fluid. Direct smear and culture of this fluid were negative. Penicillin was instilled, however, the patient's condition remained the same throughout May 8, and early May 9, 1946. He was extremely restless, complaining almost constantly of pain and asking for water. His skin and extremities were mottled and cyanotic and the skin was cold and clammy. The patient was disoriented and irrational and difficult to restrain.

At 9 30 A M on May 9, 1946, the patient's temperature suddenly rose to 105.6 degrees F by rectum where as his previous temperature had been 99 degrees F. At this point, it became extremely difficult to count his pulse and his respirations rose to 40-44 and his blood pressure fluctuated slightly but always at shock levels. He was continued on a supportive therapy. An attempt was made to restore his blood chemistry to normal. The patient was obviously going rapidly down-hill from extensive and overwhelming sepsis.

At 2 00 P M on May 9, 1946, the patient was taken to the operating room and under local procaine infiltration, a posterior mediastinotomy was done as a desperate measure in a nearly moribund patient in profound shock. A four-inch paravertebral incision was made. The erector spinae muscle group was retracted. Two-inch segments of the 9th and 10th ribs were removed subperiosteally and the posterior mediastinum was entered. There was evidence of extensive mediastinal infection with a large rent present in the left pleural membrane. There was a small similar tear in the right pleural cavity. Both of these openings were widely enlarged for free drainage. The actual point of perforation of the esophagus could not be determined. The cavity was then packed with hydrogen peroxide sponges followed by a dry sterile dressing and adhesive strapping. The closed intercostal drainage tube was kept in place. Immediately after this procedure the patient seemed much relieved, he was, of course, returned to the ward with an extremely poor prognosis.

One hour after his return to the ward his condition deteriorated. Respirations were 40, blood pressure was unobtainable and his pulse

could not be counted. A continuing effort to elevate the blood pressure was made with whole-blood transfusions, this continued to be unavailing and oxygenation by mask was inadequate. Two hours after his return from the operating room there was no response to stimulants and the patient expired at 4 15 P M on May 9, 1946.

Three hours later, post mortem examination revealed a longitudinal laceration of the esophagus in its distal portion on the left posterolateral aspect approximately one-half centimeter above the cardia. *B. Coli Communis* was cultured post mortem from the heart's blood and right and left lower lobes. There was dissection of the esophagus 15 cm upward above the laceration and air bubbles in the surrounding mediastinal tissues. Pressure on the stomach pushed gastric contents into the left pleura.

Microscopically, the esophagus, at the point of rupture, revealed an acute inflammatory reaction with tissue necrosis and blood vessel thrombosis extending through even the outermost layers and involving the peri-esophageal tissues as well. The laceration was approximately three centimeters in length and associated with (1) intramural and peri-esophageal abscess formation, (2) severe mediastinitis with mediastinal emphysema, (3) bilateral severe pleuritis, (4) subcutaneous emphysema, (5) passive congestion liver, (6) atelectasis left lower lobe, (7) minimal pericardial effusion.

Treatment

Following a spontaneous perforation of the esophagus, the patient's course generally is progressively and rapidly downhill. Time is of the essence in undertaking to treat this condition. The most important single factor is the time interval between the occurrence of the rupture and the placing of the patient in the hands of the Thoracic Surgeon. It is our belief that operative maneuvers such as closed intercostal drainage and posterior mediastinotomy are measures of procrastination and will probably not be successful in saving one of these patients except under very unusual circumstances. A bona fide case of spontaneous perforation of the esophagus with fulminating sequelae will run a rapidly fatal course in spite of measures such as these. These patients almost from the moment they are first seen, are so seriously ill, so obviously prostrated and so nearly moribund that one's first impulse is to consider their prognosis hopeless and to undertake only to make them comfortable insofar as possible. This policy in the past, aside from the problem of diagnosis, has led to a 100 per cent mortality. Regardless of the condition in which the patient is first seen, we believe that it is of the utmost importance to quickly render the patient whatever supportive treatment is possible and undertake definitive treatment at once. No matter how acutely ill the patient appears at that time, he will show no further improvement and within a matter of hours his condition will rapidly deteriorate as signs of sepsis and toxicity develop.

To our minds then the procedure of choice in a spontaneous perforation of the esophagus is an open thoracotomy with endotracheal anesthesia, adequate oxygenation and positive pressure as indicated. The mediastinum should be widely opened and decompressed into the left pleura. If the right pleura is grossly contaminated this should also be widely opened. The laceration of the esophagus can be rapidly closed with an inverting mucosal suture of catgut followed by interrupted silk sutures, thus obviating further contamination. The anesthetist should then expand the lungs, the right chest should be sucked out during this process and the chest closed tightly with the left pleura drained by an adequate underwater seal drainage system. The cardio-pulmonary physiology is thus restored to as nearly normal a situation as possible and the patient is given his maximum possible chance to combat infection.

Supportive measures as an adjunct to thoracotomy (1) *Oxygen* delivered either by nasal catheter or preferably by a positive pressure mask (2) *Adequate fluids parenterally* including the liberal use of whole-blood (3) *Massive doses*, 200,000 to 500,000 units, of *penicillin* in both the right and left pleural cavities and in addition 100,000 units of penicillin intramuscularly every three hours should be given (4) *Streptomycin* may be given during the acute phase probably in a dose of 0.5 grams every six hours to help combat the mixed infection realizing that later the organisms may develop resistance to the drug (5) *Sulfadiazine* therapy may or may not be practical parenterally depending upon the urinary output (6) The *patient* should be made as comfortable as possible by adequate doses of demerol although morphine may be necessary (7) *Nothing by mouth* for 24 to 36 hours (8) The *mouth and throat* should be sprayed with penicillin solution, 10,000 units to the cubic centimeter giving approximately 1 cc every two hours until the esophageal laceration is closed. At the same time, careful mouth care should be given to the patient (9) *Abdominal distention* may be combated by the usual measures, flaxseed poultices or hot-water bottles, prostigmine, and rectal tubes (10) If the *left pleural cavity* is drained, the right pleural cavity should be considered as potentially infected even if no tear exists and a *right thoracentesis* should be done once or twice daily as indicated by the portable chest roentgenogram and intrapleural antibiotics given. Irrigation of the drainage catheter through a Y tube may be carried out every two hours if necessary. Penicillin and streptomycin diluted in saline should be used as the irrigating fluid (11) If *mediastinal emphysema* is severe with paradoxical pulse and obstructed inflow to the right heart, a simple collar incision may be done as the patient lies in bed.

A finger introduced into the anterior superior mediastinum will suffice to effect decompression (12) *Competent nursing* care is essential

SUMMARY

1) Spontaneous perforation of the esophagus is a distinct clinical entity, in which, sudden rupture through all layers occurs in the lower end of a normal esophagus

2) The diagnosis has been rarely made during life so treatment could be instituted. The mortality until very recently has been 100 per cent

3) Rupture occurs usually in a middle aged, alcoholic male

4) The laceration classically occurs in the lower one-fifth of the esophagus, in a longitudinal direction and on the left posterolateral aspect and is sharp edged and incised in appearance. Mediastinitis, empyema and pneumothorax usually result immediately

5) Chest roentgenograms, thoracentesis and subcutaneous emphysema will enable one to make a correct diagnosis

6) A case report of a patient unsuccessfully treated is presented

7) On the basis of laboratory experiments a rationale of treatment is suggested involving supporting care with early thoracotomy and suture closure of the laceration

Note The authors wish to express their appreciation to Doctor Stephen S. Maddock, Director of the Surgical Research Laboratory of the Boston City Hospital for his cooperation, and advice in this study

RESUMEN

1) La perforación espontánea del esófago es una entidad clínica clara, en la que la ruptura repentina, a través de todas las capas, ocurre en la extremidad inferior del esófago normal

2) Sólo con rareza se ha hecho el diagnóstico durante la vida para permitir que se aplicara el tratamiento. Hasta muy recientemente la mortalidad ha sido del 100 por ciento

3) Generalmente la ruptura ocurre en un hombre alcohólico de edad mediana

4) Clásicamente, la ruptura ocurre en el quinto inferior del esófago, en una dirección longitudinal y en el aspecto posterolateral izquierdo, y tiene un borde agudo y que parece cortado. Mediastinitis, empiema y neumotorax generalmente resultan inmediatamente

5) Los roentgenogramas torácicos, la toracentesis y el enfisema subcutáneo facilitan el diagnóstico correcto

6) Se presenta un informe sobre un caso que fue tratado con mal éxito

7) A base de experimentos de laboratorio se sugiere un tratamiento que consiste de cuidado sustentante, con toracotomía temprana y sutura de la laceración

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Chronic Constrictive Tuberculous Pericarditis*

Report of a Case with Pericardiectomy

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As its name implies, this disease is distinguished by an inflammatory and cicatricial transformation of the pericardium, trapping the heart in a compressive, inelastic envelope. The deposition of scar tissues may incarcerate the heart, fix the heart and pericardium to unyielding surrounding structures and constrict the great veins and aorta. Clinically, the predominance of any or all of these features will have its peculiar bearing on the disease.⁵ The cumulative result is circulatory failure from deficient filling of the heart. The problem seems to stand clear in its simplicity—the removal of a mechanical obstruction, a familiar task to the surgeon. Unfortunately, the location of the involvement, its etiology and the wretched condition of the patient makes this task formidable indeed.

The organism held frequently responsible for constrictive pericarditis is the tubercle bacillus.¹³ Blalock and Burwell² demonstrated a tuberculous etiology in 18 of 28 cases. Three cases were due to pyogenic organisms. Harrington⁶ found tuberculosis in 5 of 21 cases. Rheumatic pericarditis rarely progresses to the chronic constrictive stage and therefore rheumatic fever cannot be incriminated. Tuberculous pericarditis usually occurs in association with tuberculosis of the lymphatics, pleura or peritoneum. The pericardium commonly becomes involved by extension of adjacent infection from caseous mediastinal or peribronchial lymph nodes. The dynamics of constrictive pericarditis follow the familiar pattern of tamponade. They were clearly described by Burwell and Blalock⁴ as (1) High peripheral venous pressure (2) Low peripheral arterial pressure (3) Basal heart rate is elevated (4) Movements of heart are diminished (5) Total blood volume is 30-45 per cent above normal (6) Circulation time is prolonged (7) Per-minute output of the heart is diminished. No significant increase in stroke volume with exercise.

The patient with constrictive pericarditis of tuberculous origin

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may present the picture of heart disease with or without parallel tuberculous activity elsewhere. Generally, the imperative nature of pericardial involvement dominates the clinical scene. Impressive features are the marked venous engorgement, hepatomegaly, recurrent ascites and pleural effusion and the small paradoxical pulse. The heart is rarely enlarged, the heart sounds are faint and murmurs are absent. Blood pressure and pulse pressure are low. Mild pulmonary congestion is paled by the marked peripheral venous distention. Dyspnea at rest is rare and when present is expressive of massive pleural effusion and ascites. The patient may be febrile and this response is an important index of tuberculous activity.

The elevated venous pressure is not appreciably altered by pleural and abdominal paracentesis. Frequent venous pressure readings give reliable objective evidence of the progress of the disease. The return of venous pressure to normal is the prime criterion of successful therapy. Radiological study of the heart is an important aid in diagnosis.^{8,11} Roentgenoscopic signs are limitation of cardiac shift with changes in position of the patient, decrease in amplitude of cardiac pulsation, and limitation of the elongation of the heart with descent of the diaphragm. Roentgenographic findings are pericardial calcification, a small aortic knob and a triangular or globular shaped heart. The x-ray kymogram gives a graphic record of the reduced excursion of the heart muscle. Opinions vary as to whether the kymogram record changes



FIGURE 1

Figure 1 Chest x-ray film preoperatively

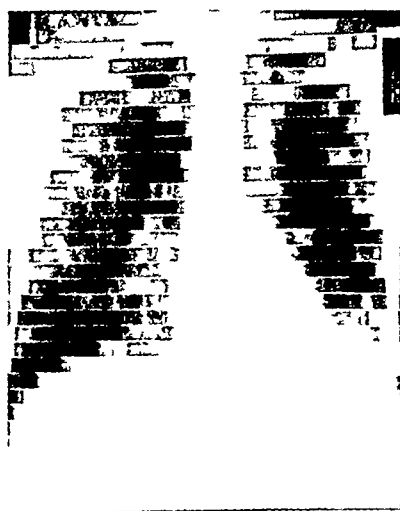


FIGURE 2

Figure 2 Kymogram eight months postoperatively

consistent with relief secured by surgery Heuer and Stewart¹¹ and White¹² have described electrocardiographic changes in chronic adhesive pericarditis These are mainly distinguished by low QRS complexes and flat T waves

Definitive therapy is the removal of the binding pericardial-epicardial scar All efforts are bent to eliminate edema and serous effusions in preparation for surgery A low salt, high protein diet is given Mercupurin and ammonium chloride are effective diuretics Large effusions may require paracentesis Digitalization is not recommended because it has been shown to decrease the per minute output of the heart in this condition Burwell³ feels that digitals may be indicated where there is auricular fibrillation, when failure of the atrophic myocardium is expected after pericardiectomy, and in the rare case that has added myocardial failure Quinidine may be used preoperatively, as in this case, to forestall ventricular fibrillation when the heart is being manipulated Conflicting opinions exist as to the necessary limits of cardiac decortication Most American surgeons advise liberating the right and left ventricles without going beyond the auriculo-ventricular groove The auricles and great vessels are avoided⁹ Some European surgeons¹⁰ are content with freeing the left ventricle Practically, the extent of decortication is dictated by the manifold dangers of adherent coronary vessels, attenuated myocardium and obliterated cleavage planes In addition, the surgeon must skirt the hazards of ventricular fibrillation and cardiac

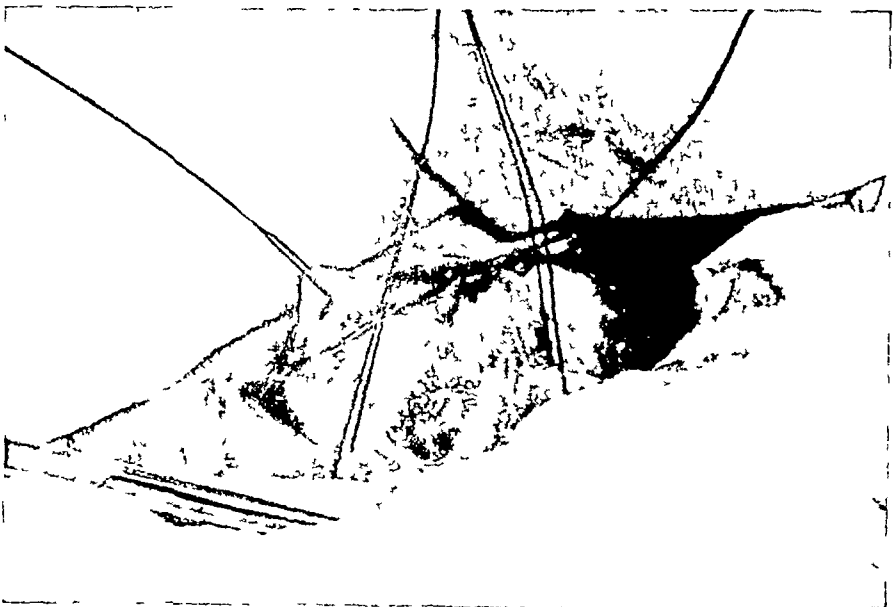


FIGURE 3 Pericardial scar at operation

ariest Hence, physiological needs are frequently subordinated to surgical caution Pericardiectomy is not calculated to, nor does it affect the basic tuberculous infection Spread and recurrence may develop after operation Appreciation of this fact is required to explain some of the dismal results in the face of adequate surgery Perhaps streptomycin will fill the need for controlling the element of infection

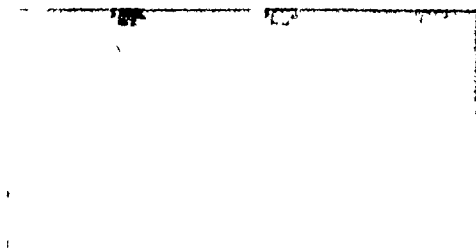


FIGURE 4 Angiocardiogram two and a half months postoperatively

The determination of the optimum time for surgery requires exquisite judgment There is general agreement that operation should be delayed until the tuberculous infection has become inactive Certainly, morbidity statistics confirm this view Unfortunately, the rapid march of compressive symptoms may dictate surgical intervention before infection has subsided The surgeon must weigh the relative influence of infection and constriction, and place most emphasis on circulatory interference

The following case is presented

The patient is a 31 year old white barber Familial and past history were not related to the present illness In January, 1947 he was stricken with a pulmonary infection alleged to be pneumonia He was treated with penicillin and remained in bed for two weeks The patient tried to resume his job, but was forced to quit working because of increasing dyspnea and weakness He had an unproductive cough There was no hemoptysis He was hospitalized at the Veterans Administration Hospital, Tuscaloosa, Alabama At that institution, his chest was tapped and about one quart of clear yellow fluid was removed His abdomen and ankles began to swell and he became progressively weaker He was transferred to the Kennedy Veterans Hospital, VAMTG on March 30, 1947

On admission the patient appeared cyanotic, dyspneic and chronically

ill His neck veins were distended The left hemithorax was flat to percussion No breath sounds could be heard over the same area The PMI of the heart could not be felt On percussion, the heart was not enlarged Heart sounds were distant There was regular sinus rhythm No murmurs could be heard Blood pressure was 80/60 The pulse was paradoxical Abdominal distention and shifting dullness were apparent Hepatosplenomegaly was present There was 2 plus pitting pretibial edema

Laboratory Findings Blood count, RBC 4.8 million, WBC 9,500, polymorphonuclears 78, lymphocytes 18, monocytes 4 Urinalysis Light amber, pH 4.5, sp gr 1.005, albumen negative, sugar negative, many fine and coarse granular casts, occasional WBC Blood chemistry total protein 6.5 per cent, albumin 3.6, globulin 2.9 Serum bilirubin 2.2 mg per cent Malaria smear negative No agglutination for typhoid, paratyphoid, brucella abortus, tularemia Blood culture sterile Urine culture, staphylococcus aureus and gamma streptococcus Pleural fluid protein 1.8 per cent, smear and culture negative for tuberculosis and other organisms, many WBC, no tumor cells X-ray film of chest moderate pleural effusion on the left Fluoroscopy massive left pleural effusion with displacement of the mediastinum moderately to the right The heart was not enlarged and no pulsations of the cardiac outline were seen Venous pressure 32 cm of water

The patient was seen by Dr Abraham Gootnick, Chief of the Cardiovascular Section who made a diagnosis of constrictive pericarditis A tuberculous etiology was entertained, but could not be proved The diagnosis was based on (1) Elevated venous pressure (2) Pleural effusion (3) Ascites and dependent edema (4) Low blood pressure (5) Paradoxical pulse (6) Absence of valvular murmurs (7) Enlarged smooth tender liver (8) ECG showing low voltage, and inverted T waves in all leads

The patient was transferred to the cardiovascular service for further study and preparation for surgery A low salt, high protein diet was given Repeated left thoracentesis and abdominal paracentesis were performed Mercurial diuretics were administered The effectiveness of these measures was limited, since the pleural effusion recurred rapidly However, ascites and peripheral edema became less marked The patient remained afebrile until April 28, 1947 when he suddenly had several bouts of fever mounting to 104 degrees F The fever was presumed to be evidence of the activation of the underlying pericardial disease Gradually, the fever reached a lower level Relief of circulatory interference, by medical means, was transitory It became evident, that despite the active infection, surgery was indicated to release the seriously compromised heart Quinidine was administered for four days and on May 15, partial pericardiectomy was performed

OPERATION

Findings The pericardium varied in thickness from 3 to 7 mm The adhesions between the epicardium and pericardium were pliable and relatively easily separated by blunt dissection There was a fairly definite band around the great vessels at the base of the heart The apex was freed completely, as was the diaphragmatic surface The pleura was very adherent on the left, and could not be stripped as completely as desired The right auricle was partially exposed The region of the superior vena cava was freed as much as possible from the left side but

could not be safely freed entirely. Apparently the inferior vena cava was released by this separation.

Procedure The patient was placed on his back. The usual skin preparation was done. A curved incision was made over the second rib extending downward to the sternum, and laterally along the 5th cartilage. This was extended through skin, subcutaneous tissue, and pectoralis muscle. Portions of the 2nd, 3rd, 4th and 5th cartilage, and ribs were resected subperiosteally. Internal mammary vessels were ligated, and incision was made through the intercostals, exposing the mediastinum. The left pleura was stripped to the left. Several holes were made and repaired with atraumatic catgut. Apparently no hole was made in the right pleura in stripping it back. An incision was made over the heart through the pericardium, and a line of cleavage was established. An incision was made at right angles to the original incision, and the flaps kept intact and carried in all directions. Excess pericardium was removed, and the heart was further freed by blunt finger dissection as far as possible. The anterolateral surface of the aorta was freed, releasing a band around the base of the heart. One per cent novocaine was dropped on the heart from time to time. The space was irrigated with saline and 200,000 units of penicillin was instilled. The wound was closed with interrupted catgut sutures with two rubber tissue drains in place, one into the mediastinum, and one anterior to the pericostum and perichondrium. The skin was closed with interrupted mattress and simple sutures of silk. The patient left the operating room in about the same condition as when the operation began.

PATHOLOGY REPORT

Microscopic Section is composed of dense hyalinized connective tissue diffusely infiltrated by mononuclear cells, epithelioid cells and occasional giant cells of the Langhan's type. Tubercle formation is widespread and most of the tubercles show caseation necrosis in their centers. In many instances the caseous necrotic areas are confluent forming larger zones in which no cellular detail can be recognized. In one section there is a rather large amount of tuberculous granulation tissue and recent hemorrhage. Near one margin the surface of both sections is covered by a fibrinous exudate. Beneath the surface the tissue is of a fibroadipose type, and contains many dilated blood vessels, neutrophils and chronic inflammatory cells.

Diagnosis Tuberculous pericarditis

Immediately postoperative, there was a marked serous discharge from the wound. Cyanosis and neck vein distention receded considerably. Blood pressure was 90/70 mm of mercury and venous pressure 15 cm of water. On the following day the patient became icteric. Within two weeks the jaundice gradually subsided. Amigen was given to replace protein lost in the serous discharge. On the third postoperative day dyspnea recurred. X-ray inspection showed a large left pleural effusion. Drains were removed and left thoracentesis was performed. Repeated aspirations of the left hemithorax were instituted to remove the rapidly accumulating fluid. Low salt diet and mercurial diuretics were resumed. Evidence of liver damage was seen in the laboratory studies. BSP 15 per cent retention in 45 minutes, cephalin flocculation 3 plus in 4 hours, serum bilirubin 1.5 mg per cent. Low grade fever persisted after healing of the wound. It was assumed to be due to active infection in

the remaining pericardium. The pleural fluid was a transudate and negative culture. On June 19, 1947 streptomycin therapy was begun. Forty grams of the antibiotic was given as 0.2 gram every four hours for five doses daily. The fever gradually subsided and he remained afebrile after July 30, 1947. The main difficulty was the ever recurring pleural effusion and edema. There was cause for alarm when the venous pressure rose to 22 cm of water on August 1, 1947. An angiocardigram showed no superior vena caval obstruction. Constriction about the caval orifice was ruled out as a cause of the venous engorgement. Kymographic studies demonstrated poor pulsations of the cardiac border. On September 26, 1947 no recurrence of pleural effusion was noted. X-ray inspection showed marked reduction in the pericardial and mediastinal thickening. The kymogram indicated increased amplitude of contractions of the left ventricle. Ascites, edema and venous distention disappeared. The enlarged spleen and liver diminished in size. Venous pressure had dropped to 7.5 cm. The patient was ambulatory and had no dyspnea on ordinary effort. On January 2, 1948 he returned from a month's leave, having gained four pounds. His liver was just barely palpable and the spleen could no longer be felt. BSP test showed no retention after 45 minutes. Cephalin flocculation was negative, prothrombin time 100 per cent, serum bilirubin 0.6 mg per cent. The ECG exhibited a normal pattern. On fluoroscopy, increased motion of the heart was seen. The patient was considered apparently cured and transferred to a convalescent hospital February 1, 1948. Following a paranoid type of schizophrenic reaction he went home in remission July 29, 1948.

Comment

This case presented some interesting and perplexing problems. The most disturbing of these was the slow recovery of the patient. Persistent anasarca and elevated venous pressure, in the face of adequate surgery, can be a source of chagrin and impatience to the surgeon. The consensus is that complete recovery can frequently not be expected for months.^{1,2,6} Apparently the liberated myocardium is atrophied and requires time to regain its strength. This is a comfortable assumption if the surgeon can be assured that no recurrent or overlooked cicatricial bands compress the great vessels and the heart. Angiocardigraphy is suggested as a method of visualizing the patency of the superior vena cava. By such means we were convinced of innocence in that quarter. In view of the subsequent recovery it may be assumed that the patient was suffering from myocardial failure in his postoperative course.

Mercurial diuretics, salt free diet, bed rest and thoracentesis were of great value in successfully weathering this precarious period. The pre- and postoperative use of these measures must be assigned a role of importance, second only to pericardiectomy.

There is no information in the literature concerning the effect of streptomycin on tuberculous pericarditis. Streptomycin was not available, here, preoperatively. Its use postoperatively may

have curbed the activity of the disease in the remaining pericardium. Possibly, it protected the open pleural cavities from the disease. These remarks are conjectural, no unequivocal conclusions can be drawn from this case as to the value of streptomycin in active chronic productive tuberculous pericarditis. Should further study prove the specificity of streptomycin, the management of this disease will be simplified. More cases of tuberculous pericarditis with effusion may progress to healing and instances of obstructive scarring may become rare. Where decortication will be required, one can envision earlier operations on cases rendered inactive by the drug. Earlier operation will mean coping with less cicatrization and a healthier myocardium. Tuberculosis of the pericardium will not lose its terrors, but streptomycin may blunt its sting.

SUMMARY

1) The clinico-pathological aspects of constrictive pericarditis have been summarized.

2) A case of tuberculous constrictive pericarditis with partial pericardiectomy and apparent cure has been presented.

3) Freeing the heart from its fibrous encasement is the initial step in the relief of cardiac embarrassment. Postoperative supportive care of the weakened myocardium is important in the total therapy of the disease.

4) Streptomycin was used postoperatively. Its value will be determined by more extensive clinical studies.

RESUMEN

1) Se resumen los aspectos clínico-patológicos de la pericarditis constrictiva.

2) Se ha presentado un caso de pericarditis constrictiva tuberculosa con pericardiectomía parcial y aparente curación.

3) La liberación del corazón de su coraza fibrosa es el paso inicial en aliviar el embarazo cardíaco. El cuidado sustentante postoperatorio del miocardio debilitado es importante en la terapia general de la enfermedad.

4) Se usó estreptomicina después de la operación. Su valor será determinado por estudios clínicos más extensos.

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Intrathoracic Sympathoblastoma

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Intrathoracic neoplasms of sympathetic nerve origin constitute a small but exceedingly interesting group of tumors. In 1943, Wahl and Robinson¹ reported the finding of only 13 cases of intrathoracic neuroblastoma in the literature. In 1946, Hollingsworth² stated that the literature disclosed 16 cases of intrathoracic neuroblastoma, to these he added the report of an additional case. Although it is claimed that the incidence rate of carcinoma of the lung is increasing, there is no statistical evidence to indicate that the same applies to intrathoracic neoplasms of sympathetic nerve origin. It would seem more likely that the steadily increasing number of patients subjected to thoracic surgery has resulted in the opportunity for more accurate pathological examination of intrathoracic tumors. It can not be doubted that, in the past, patients with intrathoracic neoplasms of sympathetic nerve origin have been erroneously diagnosed, on the basis of x-ray examination alone, without subsequent histological study. We may thus expect that an increasing number of cases of intrathoracic neoplasms of the sympathetic nervous system will be reported in the future.

There has been a good deal of confusion in the classification and in the nomenclature of tumors of sympathetic nerve origin. The situation has been further complicated by the fact that the tumors frequently contain cells of different types, all of sympathetic nervous system origin, but some of undifferentiated type and others of mature cell type. One can thus appreciate the possibilities of difference in opinion and interpretation among pathologists. In regard to nomenclature, it now appears that different descriptive terms have been applied to tumors of essentially the same pathological type. In the literature there are reports of tumors variously designated as neuroblastoma, sympathoblastoma, sympathicoblastoma and neurocytoma, which apparently have been applied to neoplasms of the same histological pattern.

Clinical Aspects In 75 per cent of cases intrathoracic sympathoblastomata are discovered in children less than ten years of age. At the time the diagnosis of an intrathoracic tumor is made, the mass is usually found to be quite large. It is thus apparent that these tumors are apt to start very early in life and one can not expect clinical symptoms to be noted until the mass

has reached such size that pressure symptoms occur or unless degenerative changes take place within the tumor mass causing cough, fever and expectoration. Hollingsworth² reported a case of the latter type, it is of interest that this patient was 39 years of age, and undoubtedly had the tumor asymptotically for a considerable period of time. In the case reported below, the credit for detecting the tumor at a relatively early age should go to the parents of the child who thought they detected a slight bulge in the supraclavicular fossa when the child cried. On the basis of this observation alone, they consulted their physician whose fluoroscopic examination revealed the presence of a large mass in the left hemithorax.

In recent years mass x-ray studies have served to bring to light many instances of pulmonary pathologic changes, chiefly tuberculous lesions in varying states and stages of clinical activity. However, one must realize that the overwhelming majority of roentgen examinations of the chest have been carried out in adults. In as much as the intrathoracic sympathoblastoma is essentially a tumor of early childhood, it would be necessary to extend the system of mass x-ray study to the younger age group in order to detect these asymptomatic tumors at the earliest possible time. As the tumor is malignant in character and as the treatment is surgical, it is quite apparent that early diagnosis is imperative to achieve the optimum therapeutic results.



FIGURE 1

CASE REPORT

S S, male, age 19 months was referred for examination on May 8, 1947

History Birth was by cesarean section Weight at birth was 8 pounds and 3 ounces The infant developed normally and has had no diseases Four weeks prior to medical consultation the parents thought that they noted a slight bulge in the left supraclavicular area when the child cried Otherwise, he seemed perfectly normal There was no cough, hoarseness or change in voice Temperature was normal The child apparently had no pain or discomfort He was examined by his physician who found a large mass in the left upper chest on fluoroscopy and referred the patient for further study

Physical Examination A normally developed child, 19 months of age, who appeared perfectly well There was no inflammatory change in the nose or throat The left chest showed a rather definite respiratory lag On percussion there was flatness over the upper half of the left thorax Heart and mediastinum seemed slightly displaced to the right Breath sounds over the left upper thorax were markedly diminished No rales were heard Breath sounds at the left base and over the right lung were normal Abdomen no masses or tenderness The spleen was not felt There was no adenopathy X-ray film there was a large dense mass filling the left upper thorax The lower border of the mass was rounded and well demarcated The heart was not enlarged but was somewhat displaced to the right side Diaphragm was normal in contour and in position The right lung showed no abnormality

Urine examination was negative Blood study was normal Blood chemistry protein 6.11, calcium 10.4, phosphorous 5.5, urea 13.0

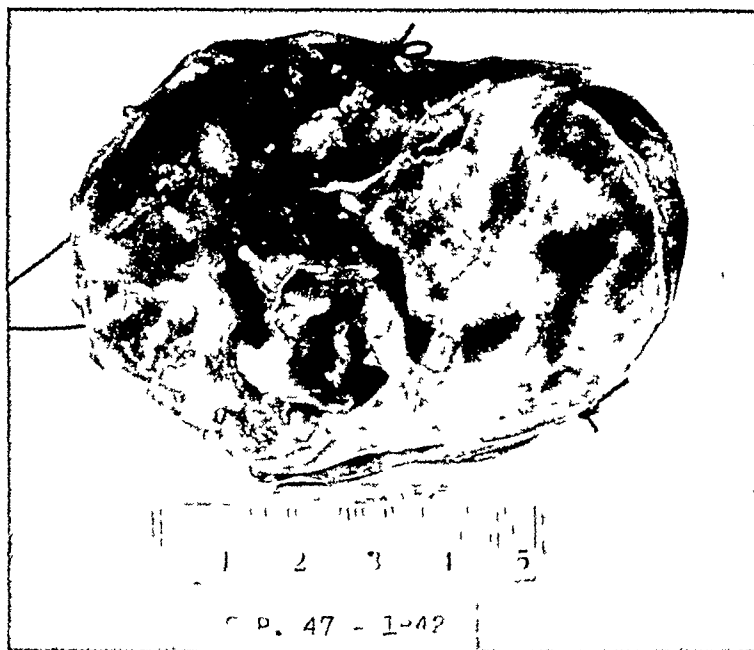


FIGURE 2

The patient was admitted to the Brooklyn Jewish Hospital for operation Operation, May 13, 1947 (Dr Henry W Louria) An oblique incision was made from the third dorsal spine to the left 7th interspace The pleural cavity was opened and a large firm mass was found apparently arising from the posterior mediastinum The 3rd, 4th and 5th ribs were cracked to obtain proper exposure The blood supply of the mass was



FIGURE 3



FIGURE 4

ligated and the entire mass freed and removed. A few glands were noted between the left carotid and the subclavian arteries. Closure interrupted chronic for ribs and pleura. Skin was closed with clips.

Postoperative Course On the first day following operation, temperature rose to 104 degrees F and the patient had several clonic convulsive seizures. He was kept in an oxygen tent for five days. Temperature was normal on the 8th day and the patient was discharged on the 12th day after operation.

Pathological Report (Dr. David Grayzell) Specimen consists of a firm mass 9.5 x 5 x 3.5 centimeters. The external surface is covered in places by a smooth and glistening capsule which is quite firmly adherent. The remainder of the external surface is dark, red-brown in color and is roughened by fibrous tabs. The entire mass is firm and the cut surface has a central homogeneous yellow-gray area which is 4 cm. in greatest diameter. This is quite sharply demarcated from the surrounding darker tissue mass.

Microscopic Examination The sections showed a variegated picture. In places the growth is composed of nests and sheets of large round cells with granular cytoplasm and large deep staining nuclei. In some areas no definite cytoplasm or cell outline can be made out. Elsewhere, the cytoplasm is abundant and the cells are polyhyal. Mitotic figures are numerous. Tumor cells are also seen within the lymphatic and vascular sinuses. The stroma is in places abundant, dense and collagenous and infiltrated with large and small mononuclear cells, plasma cells and polymorphonuclear leucocytes. In some areas the cells appear elongated and are deeply stained. With the Nissl stain, delicate processes are seen arising from some cells as well as granules in the cytoplasm.

Diagnosis Neuroblastoma, mediastinal

The child was referred for postoperative x-ray therapy. Films taken two and one-half months, and seven months after operation show no evidence of any tumor mass. The child appears perfectly well. There is no cough, fever or other symptom.

SUMMARY

A case of a clinically asymptomatic intrathoracic sympathoblastoma is reported in a child 19 months of age. The tumor was successfully removed. Eleven months after operation the child is apparently well, x-ray studies reveal no evidence of recurrence.

Routine roentgenologic studies of the younger age group will probably result in the discovery of more tumors of this type and will bring them to light at a time when surgical removal can be carried out with favorable results.

RESUMEN

Se informa sobre un caso de simpatoblastoma intratorácico, clínicamente asintomático, en un niño de 19 meses de edad. Se extirpó el tumor con buen éxito. Continúa el niño aparentemente bien.

once meses despues de la operación Los estudios radiograficos no revelan signos de recidivas

Estudios roentgenológicos de rutina de los grupos etarios mas jovenes probablemente resultaran en el descubrimiento de mas tumores de este tipo y los revelaran en una época en la que es posible realizar la extirpación quirurgica con buenos resultados

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Bronchial Lavage in Tuberculosis

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The tuberculosis surveys we have been making since 1940 have proved once again the incompetence of radiological examination alone to affirm or deny the etiology of pulmonary disease in persons who have no expectoration and in patients with early tuberculosis. In view of this, we decided to obtain bronchial secretions directly from the bronchi through bronchoscopy. This method we had to give up on account of the annoyances and unsatisfactory results obtained with this procedure. Examination of the fasting gastric contents for tubercle bacilli was also found inaccurate and unreliable.

In 1943 we performed the first bronchial lavage using the technique we had developed for bronchographies since 1934.

Technique

The subject should be examined not sooner than from three to four hours after his last meal. He is seated on a chair in front of the physician, puts his tongue out and holds it in this position by means of a piece of gauze. He is told to breathe only through the wide open mouth. Light local anesthesia is established with a 1 per cent pontocaine solution by swabbing the tonsils, uvula and the posterior wall of the pharynx. After anesthetizing the throat, we pass through the nose a No. 14 Nelaton catheter, the tip of which will reach the oropharynx. The catheter is not introduced into the larynx or into the trachea. A 20 cc syringe containing 5 cc of pontocaine solution is connected to the catheter. Pontocaine is instilled drop by drop through the catheter in such a manner that it drops on the posterior wall of the pharynx. Thus it reduces the cough reflex, since we need to control it so that the patient may be able to cough at the right moment. For the anesthetic instilled through the catheter to reach the bronchus, it is essential that the patient breathes deeply through the mouth and avoid coughing.

Once the anesthetic is instilled, the patient must lie on his side, according to the location of lesion, with his head a little higher than his chest. In this position, we instill through the catheter, 15, 20 or 30 cc of tepid, isotonic saline solution to obtain

*Presented at the 14th Annual Meeting, American College of Chest Physicians, Chicago, Illinois, June 20, 1948.



FIGURE 1

FIGURE 2

FIGURE 3

Figure 1, First Stage The patient has her mouth open, breathing deeply through it, and with her tongue protruding and held by her own hand. The doctor anesthetizes her pharynx, swabbing same with a 1 per cent solution of Pantocaine. Note the position of the patient (especially the open mouth, and her tongue held with a piece of gauze). —*Figure 2, Second Stage* The patient in the same position breathing steadily through her mouth, holding her tongue with her own hand with a piece of gauze. The Doctor passes a nasotracheal catheter number 14 through one nostril only until it reaches the cavum. —*Figure 3, Third Stage* The patient in the same position, breathing steadily through the open mouth. A syringe containing 2 cc of 1 per cent pantocaine is connected with the catheter and the anesthesia is instilled, drop by drop, by the doctor. The patient is made to breathe deeply and strongly so that the anesthesia may pass into the bronchi. This stage may be effected with the patient lying down, if desired.

expectoration When the isotonic saline solution has been in the bronchus for 2 or 3 minutes, the patient will feel a strong urge to cough At this moment, we give him a measure glass for sputum He is told to cough vigorously This expels the saline solution, together with quantities of bronchial secretions and inflammatory exudate from the lung The material collected in the measure glass contains few Koch bacilli and for this reason, it must always be submitted to concentration method before microscopic examination, culture and guinea pig inoculation

With this technique we have found that 90 per cent of tuberculous lesions were discharging Koch bacilli In a number of cases with minimal lesions and with no symptoms, we have demonstrated the presence of Koch bacilli We have carried out bronchial lavages for a great number of persons, who were living in close contact with tuberculous patients with Koch bacilli in the sputum The former did not show shadows in the chest roentgenogram, still by the lavage, we have found that 10 per cent of them had Koch bacilli

It is recommended to make bronchial lavage for all persons, who, with no x-ray shadows, are living together with persons

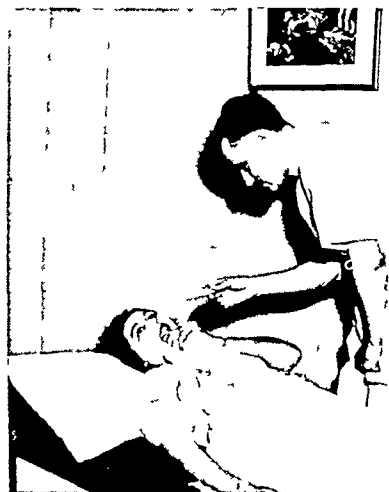


FIGURE 4



FIGURE 5

Figure 4, Fourth Stage The patient lies down on a chaise lounge, with her head a little higher than the rest of her body The mouth is kept open and deep breathing continued The Doctor has charged the syringe with 20 cc of tepid natural saline solution and instillates it slowly through the catheter to make a real bronchial lavage At this time he warns the patient not to cough and to retain the solution in the bronchi one or two minutes—*Figure 5, Fifth Stage* When the solution instilled into the bronchi has increased the desire to cough until it can no longer be controlled, at once a graduated cup is offered, into which she coughs strongly in order to collect the instilled solution and the expectoration

with tubercle bacilli in their sputum, in order to discover bronchial or tracheal lesions of tuberculous nature in time. For us, bronchial lavage constitutes the best means for establishing the activity, inactivity or cure of a tuberculous process, as well as to discover bronchial tuberculosis in those persons with normal radiographs.

All surveys or collective examinations should include search for the possible tuberculous etiology of bearers of shadows. Bronchial lavage is a valuable complement of the radiographic examination. Radiography alone occasions many errors, thus it may leave without medical care numerous cases who constitute dangerous sources of contagion to society.

SUMMARY

1) During the period of 1945-1948, 2,414 bronchial lavages were performed in Cuba. This number includes 614 bronchial lavages done by the author with his own technique. Of these, 500 cases were carried out at the Furbush Dispensary and 114 at his private office.

2) In 45.4 per cent of moderately advanced cases, considered as cured and already discharged, tubercle bacilli were still found by bronchial lavages. X-ray films in these cases showed evidence of fibrosis only.

3) We found Koch bacilli by bronchial lavage in 17 per cent of moderately advanced cases considered as cured and already discharged, with negative x-ray findings.

4) In minimal lesions without expectoration, we found 90 per cent positive with bronchial lavage.

5) Ten per cent of contact cases without x-ray evidence were found positive by bronchial lavage.

6) In a group of 90 cases of bronchial asthma, pulmonary cancer and bronchiectasis, tubercle bacilli were not found by this method.

RESUMEN

1) Durante el periodo de 1945 a 1948, se llevaron a cabo en Cuba 2414 lavados bronquiales. Este numero incluye 614 lavados bronquiales llevados a cabo por el autor con su propia técnica. De estos, se llevaron a cabo 500 casos en el Dispensario Furbush y 114 en su oficina privada.

2) En 45.4 por ciento de casos moderadamente avanzados, que se consideraban curados y ya dados de alto, todavéa se encontraron bacilos tuberculosos mediante lavados bronquiales. Las películas radiográficas en estos casos sólo mostraron signos de fibrosis.

3) Encontramos bacilos de Koch por lavado bronquial en el 17 por ciento de casos moderadamente avanzados con hallazgos radiográficos negativos

4) En lesiones mínimas sin expectoración, encontramos positivos al 90 por ciento con el lavado bronquial

5) El 10 por ciento de casos de contacto sin signos radiográficos, se hallaron positivos con el lavado bronquial

6) En un grupo de 90 casos de asma bronquial, cancer pulmonar y bronquiectasia, no se encontraron bacilos tuberculosos con este método

Cerebral Air Embolism Associated with Spontaneous Pneumothorax*

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A review of current and past literature reveals that the occurrence of air embolism following spontaneous pneumothorax is sufficiently rare to justify reporting Myers et al,¹ in 1938 presented a comprehensive paper on the subject of air embolism and spontaneous pneumothorax complicating artificial therapeutic pneumothorax but cited no instance where an air embolism and spontaneous pneumothorax occurred simultaneously

Blumberg² in 1940 described a case in which there was cerebral embolization as well as subcutaneous emphysema resulting from spontaneous pneumothorax In contrast to Blumberg's patient, where the diagnosis was established primarily by autopsy, the diagnosis in this case was established by clinical and laboratory methods

Case History and Course

The patient H Z is a 50 year old white male who entered the National Jewish Hospital in July 1943 The admission examination showed the presence of bilateral apical and sub-apical tuberculosis Bilateral pneumothorax was induced with a resulting bilateral effusion six months after induction At no time was the fluid positive for tubercle bacilli Right pneumothorax was discontinued in August 1945 and left pneumothorax in May 1946 Hospital course was uneventful until September 4, 1947 when patient became unconscious while shaving and fell to the floor The total period of unconsciousness was about 15 minutes Examination, which was carried out almost immediately, showed a motor aphasia, some weakness in the right arm, there were, however, no pathological reflexes present Blood pressure remained unaltered at 114/84 Spinal tap was negative and subsequent culture for acid-fast organisms showed no growth

On the following day the patient was found to have a right Babinski reflex as well as sustained ankle clonus There was some alteration of the sensory modalities in the right arm laterally and on the malar surface of the right cheek A chest x-ray film revealed a spontaneous pneumothorax on the right with some fluid obscuring the costo-phrenic angle The next day the patient, following a period of emotional lability in which he hurled a glass of water out of the room into the corridor,

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suddenly lost his motor aphasia. The Babinski was still present in the right foot.

On September 9th, the left pupil was found to be larger than the right. The "snout reflex" of Waitenberg, indicative of non-specific encephalopathy, was positive. The Babinski was negative and the sensory modalities appeared to be intact. Fluid obtained from the right pleural space was positive for tubercle bacilli. An electroencephalogram showed no evidence of epilepsy or localized cortical pathology. At this time he began to run a toxic febrile course and fluoroscopy revealed increase of fluid in the right pleural cavity. Manometer readings were atmospheric before and after aspiration of fluid and air, thus justifying a diagnosis of patent bronchopleural fistula. Thoracotomy was performed with subsidence of toxicity. Since then, the course has been one of slow deterioration.

Discussion

The following clinical entities were entertained in the differential diagnosis to explain the neurological signs: Tuberculous meningitis, epilepsy, cerebral embolism, hemorrhage, or thrombosis and cerebral air embolism associated with spontaneous pneumothorax. Meningitis was ruled out with the absence of typical spinal fluid findings. The electroencephalogram was normal. Gibbs et al³ in a large series of unselected epileptics found dysrhythmias in over 80 per cent of those over 20 years of age. Those under 20 years showed EEG changes in over 90 per cent of the cases. According to Busse and Ebaugh⁴ better than 90 per cent of patients suffering from petit mal have disturbed electroencephalograms. In the absence of former history and the findings described, epilepsy was discarded as a plausible diagnosis. Cerebral hemorrhage and thrombosis tend to occur in individuals with hypertension or generalized arterio-sclerosis, neither of which are present in this patient. The neurological disturbances are apt to be of longer duration than in our case. It was felt therefore that this diagnosis would not account for the picture seen.

Cerebral air embolism best explains the symptom complex observed. The occurrence of spontaneous pneumothorax and cerebral accident were to be co-related to be coincidental. The negative EKG, EEG, and spinal fluid all indicate that the factor causing the cerebral accident was fleeting in nature and quickly absorbed.

SUMMARY

A case of cerebral air embolism following spontaneous pneumothorax is described.

RESUMEN

Se describe un caso de embolia gaseosa cerebral consecutiva a un neumotórax espontáneo.

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Dusts of Clinical Significance

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Dusts and the diseases and disabilities they cause must always be of interest and importance to the family physician, chest surgeon, and industrial physician. The family physician usually sees the patient first, the chest surgeon on occasion may find his patient's health influenced directly or indirectly by dust, the industrial physician is concerned with prevention of any and all forms of dust diseases. All of them must meet the problems of differential diagnosis. Dust diseases as a class are contracted almost entirely from exposure during work.

Dusts are solid particles of such minute size that they can be picked up and moved easily, even by minor air currents. We may include the dusts derived from mining, crushing, stamping, grinding various rocks and ores containing silica and asbestos. We may include toxic dusts such as those containing lead, arsenic, and other inherently poisonous materials. Further there are fumes, defined as streams of very fine metal particles arising when certain metals are heated, examples being zinc oxide, copper oxide, magnesium oxide, lead, lead oxide, manganese dioxide. Other dusts, common in Texas, are sulfur, carbon black, antimony, lime stone. Likewise, we should mention those dusts, organic in origin, such as pollens, which produce allergic reactions on skin, bronchial musculature, or other parts of the body. Another organic dust is cotton, during the various phases of milling, spinning, and weaving. And finally there is the subject of dust as a vector or vehicle, dust not noxious per se but as a means of bringing infection into the body, germs which can cause havoc by riding in on the solid particles of some dust.

It is easy to believe that dust which is carried into the lungs in inspiration might cause harm in several ways, such as,

- 1) The fibrotic responses some of them provoke
- 2) Increased susceptibility to infections such as tuberculosis
- 3) Providing a vehicle for entry of pathogenic organisms
- 4) The inherent toxicity of the materials,

yet the number of dusts concerned in such reactions is not great so far as known today. Certainly dusts may have significance more than is yet recognized and so the subject should be re-examined frequently. On the other hand, it is possible to arouse

fear and unnecessary anxiety by undue stress upon data too little understood

By all odds the most important dust is silica, considered in the light of both the first two points above. As is well known, exposure to dust containing SiO_2 in particle size under 5 micra in sufficient quantity over a sufficient time can provoke chronic interstitial pneumonitis which progresses to fibrosis of a nodular character and may result in impairment of pulmonary function. We know very little about what a sufficient quantity is. The amount of time required undoubtedly varies with individuals, possibly with particle size. Degree of fibrosis from what seems to be similar exposure also is unpredictable. Another variant is the degree of dyspnoea from proportionate amounts of fibrosis.

In spite of these many doubts, it is agreed that dusts containing SiO_2 from certain sources, notably mining of hard siliceous rock (copper, gold, silver, zinc, iron, and hard coal), quarrying granite, sandstone, quartz, slate rock, and crystal, ceramic industries, and abrasives such as sand, sandstone, sandpaper, scouring material, soaps, brick making, if silica is used, stone finishing, construction of tubes, tunnels, aqueducts, certain types of spraying jobs, all these in certain instances have resulted in silicosis to a greater or less degree of crippling. The diagnosis is made on the history of exposure, and x-ray findings of the characteristic nodular shadows. Some cases are discovered before serious reduction of vital capacity has developed. Such patients, if removed from further exposure, may live out their lives in comfort. Reduced vital capacity is not returned to normal or even lessened by any means now known. Prophylaxis by aluminum metal powder and lately by aluminum hydroxide offers some hope and in the opinion of some, these agents may be useful therapeutically though many others doubt this latter use.

One of the most serious aspects of silicosis is its association with tuberculosis. It is agreed that the presence of the two in the same individual means a prognosis poorer by far than if they are not combined. Probably the most serious part of the association of these two conditions lies in the fact that when combined the possibility of treatment and control is reduced seriously if not lost completely.

The other phases of silicosis have been covered adequately so many times that further consideration here seems unnecessary. It is still the best example of that group of diseases known as the pneumoconioses. Let us turn to some of the dusts less well known.

First of these may well be asbestos which is a dust related because it is hydrated magnesium silicate. The hazard is en-

countered not in the use of the product but in mining, handling, and crushing the ore, and in the manufacture of various asbestos products. When inhaled in sufficient quantity, this dust produces pulmonary fibrosis which is diffuse, peribronchial, and basal at first, but may extend to all parts of the lungs as the exposure continues. Diagnosis of asbestosis in its early stages is not easy, but is made on history of exposure together with a somewhat diffuse fibrosis of lung fields, in some cases a "ground glass" appearance, with obscuring of vascular and lung markings.

Treatment is unsuccessful in reducing the involvement. Exposure should be stopped but even so there is a tendency for symptoms to become worse progressively. The only effectual control is prevention.

Another dust, common in Texas, which might be important is cotton. Yet the case against cotton is not at all clear cut. English and continental authors have been writing about byssinosis and describing chills, dyspnea, fever and other symptoms for years. True these symptoms are reported only in those workers who are required to remain in atmospheres heavy with cotton dust over long hours, chiefly indoors. Cotton pickers for example, seem to be little affected.

When it does occur, there is dyspnea, rather asthmatic in type, a dry cough with a very little expectoration of a thick tenacious mucus. There is a tendency for these symptoms to clear on discontinuing work in cotton dust, on vacations, and even over the week-end. In fact, some of the symptoms are listed occasionally under the name of Monday fever. It is uncommon to find any evidence of fibrosis at necropsy of persons who have been exposed to cotton dust for years.

In Public Health Bulletin No. 297, issued by the Federal Government, the case against cotton is reviewed for 72 pages and 249 references are listed. It states that the "dust hazard in the cotton industry may be considered to be the most important in relations to affections of the respiratory tract." Histamine in variable quantities has been found. Several potentially harmful constituents have been noted, such as gossypol, a lipid, and a protein substance unnamed. There is the inference that this is derived from bacteria, such as *aerobacter cloacae*. Insecticidal residues or disintegration products may be considered as also the high content of molds, bacteria, and spores. In general reports going back to 1818 show that illness from all causes to be commoner in cotton workers than in the general population. This is especially true of respiratory diseases. But there is progressively less differentiation as the reports become more recent, suggesting that possibly general health conditions have been improving.

Another side of the general picture, not usually considered as dust, is that of fumes. Let us hasten to add the definition which some authorities insist upon, that a fume is a stream of solid particles of extremely minute dimensions, such as arise in welding. The word is often used to mean vapors or clouds of material in a gaseous state. Such is not our meaning here. During welding such as the electric welding which was used so extensively during the war, the rod is melted by the electric current, and joins two metal surfaces. In the process, a stream of fine metal particles, actually solids, arises and often because of cramped quarters or the position of the operator, is breathed into the lungs. The effects, if any, depend upon the degree and time of exposure and upon the metals used in the rod, especially in the coating of the rod. Welder's siderosis shows metal deposits in the parenchyma and increased bronchial and hilar shadows. The importance of this lies not in mortality or morbidity, for this type of siderosis seems fairly innocuous, but rather in the danger of confusing the lung picture with more serious disease.

Perhaps one of the newest developments in the picture of dust diseases is the present interest in beryllium. The cases which have been labeled beryllium poisoning have occurred in industries which mine, grind, prepare or use beryllium in crushed or powdered form, for example, in the preparation of fluorescent screens for x-ray machines, and in the making of fluorescent lamps. The diseases associated with beryllium consist of a form of acute pneumonitis, irritation of the upper respiratory tract, skin, and eyes, and a pulmonary granulomatosis. They may be fatal, but usually are not.

Beryllium pneumonitis occurs among workmen who cut the metal on grinding wheels, and may occur in any one who has been exposed to beryllium metal or salts, especially the acid salts, in a fine dust for several weeks. It may occur during or even 2 to 3 weeks after exposure has finished. It comes on as a dyspnea, with or without fever, reduced vital capacity, substernal distress, and may have circulatory embarrassment. Many persons recover slowly. Possibly the powdered metal irritates and causes vascularization and widespread alveolar effusion, which often clears up slowly and completely. Treatment is supportive and symptomatic.

SUMMARY

Although many dusts may cause disability in isolated instances and many others may prove to be of considerable significance upon further investigation, the one dust of great and known hazards is silica. The other chemically related dust, asbestos, is known to cause great disability. On the other hand, silica in non-

crystalline or gel form, at least in commercial mixtures with aluminum hydroxide, appears to have little if any fibrogenic qualities. Here is an interesting and probably important problem, why do SiO_2 crystalline and SiO_2 gel give such different results in terms of fibrosis of the lungs?

Cotton dust is considered to be noxious but variable in its effects and, in general, the case against cotton is not clear-cut. Beryllium grinding, stamping, polishing, and crushing produces a dust which has given even fatal pneumonitis. This hazard is recently recognized, but the industry is not widespread.

Methods are available to eliminate dust exposure entirely or to a degree sufficient to avoid serious consequences. Most companies have installed or provided safety equipment. A problem still not solved is to get all workers to use the equipment consistently.

RESUMEN

Aunque muchos polvos pueden causar incapacidad en casos aislados y muchos otros podrán demostrar tener considerable significado cuando se les investigue más a fondo, el polvo de gran y conocido peligro es la sílice. El otro polvo, el asbesto, relacionado químicamente a la sílice, también se conoce que causa gran incapacidad. Por otro lado, la sílice en forma no cristalina, esto es, en forma gelatinosa, por lo menos en mezclas comerciales con hidróxido de aluminio, parece tener o pocas o ningunas cualidades fibrogenéticas. He aquí un problema interesante y probablemente importante, ¿por qué es que el SiO_2 cristalino y el SiO_2 gelatinoso dan resultados tan diferentes en cuanto a la producción de fibrosis en los pulmones?

Se considera que el polvo de algodón es nocivo pero variable en sus efectos y, en general, el pleito contra el algodón no es claro. La pulverización, trituración, abrillantamiento y molienda del glucinio produce un polvo que ha causado neumonitis hasta fatal. Se ha reconocido este peligro recientemente, pero la industria no es muy extensa.

Existen métodos disponibles para eliminar la exposición al polvo por completo o hasta un grado suficiente para evitar las consecuencias graves. La mayor parte de las compañías han instalado o suministrado equipo salvo. Un problema todavía no resuelto es hacer que los trabajadores usen consistentemente el equipo.

The Use of Bronchoscopy in Bronchiectasis*

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Bronchiectasis is a serious, progressive, and widespread disease, which carries a high morbidity and mortality, and should be recognized as such. Its management depends on a sound knowledge of disease of the entire respiratory tract, and involves medical, bronchoscopic, and surgical treatment.

Bronchoscopy is a necessary adjunct in diagnosis and treatment, and although it now is occupying a diminishing role with the advances of iodized oil bronchography, chemo- and antibiotic therapy, and surgery, it still has much to offer. This is particularly true in the field of prevention, for by its use in the treatment of known predisposing causes, many cases of bronchiectasis are prevented. The increasing success of thoracic surgery in the treatment of intrathoracic diseases has no better example than the cures now possible in victims of bronchiectasis, and bronchoscopy has contributed no small part to this success.

Neither bronchoscopic nor routine roentgenographic examination will establish a diagnosis of bronchiectasis. But the information obtained from them in addition to the information obtained from iodized oil bronchograms will establish an exact diagnosis.

The appearance of the mucous membranes, as viewed endoscopically, varies widely. In most cases there is a red, swollen membrane, particularly in the bronchi serving the involved broncho-pulmonary segments, or there may be a marked acute bronchitis if the examination is done at the time of an exacerbation, so common in these patients. The membrane frequently bleeds easily, but rarely profusely, under instrumental manipulation. At times the orifices to the secondary bronchial divisions may be found occluded by an edematous membrane or by actual granulation tissue.

The amount and character of the bronchial secretions encountered during bronchoscopy may be influenced by the severity of coughing induced by the induction of topical anesthesia to the pharynx and larynx, and since the preservation of an active,

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productive cough is desirable, both for diagnostic and therapeutic reasons, tracheal and endobronchial anesthesia is not advised. Candidates for bronchoscopy will frequently expectorate such large quantities of heavy purulent material while the pharynx and larynx are being anesthetized that only small amounts will be found within the bronchial tree on examination. However, in most cases the lobar distribution of the disease can be determined by observing the individual bronchial orifices during forced coughing. This fact is extremely important in deciding which side harbors the more active infection in bilateral cases, apparently suitable for operation. Quite frequently we have encountered cases in which the bronchograms showed equal distribution of disease in each lower lobe, but on bronchoscopy the secretions were found to arise almost wholly from one side. Obviously such information is of paramount importance in selecting the proper side for initial resection. One such case is illustrated (Fig. 1).

There is one bit of information derived from bronchoscopy that has never been fully emphasized heretofore in the literature. This is the odor emitted through the bronchoscope. A large percentage of our bronchiectatic patients will not complain of any odor to their sputum or breath, and no physical examination nor odor will be detected. Even a direct sniff of the sputum cup may not reveal an unpleasant odor, but with the bronchoscope in the involved lung, an unmistakable, foul odor is noticed, which signifies a necrotizing infection and is therefore of considerable diagnostic and prognostic value.

The value of inspection and biopsy of the bronchial mucosa is too often overlooked in obvious cases of bronchiectasis. The diagnosis seems so certain in many cases that one is tempted to omit a direct examination, which may disclose an unsuspected foreign body, neoplasm, or other obstruction. It is our belief that all patients with this disease should be bronchoscoped, if for no other reason than more accurately to establish a complete diagnosis. Two cases of bronchiectasis, one of unsuspected foreign body origin and one associated with carcinoma, are illustrated in Figures 2 and 3. Both of these diagnoses would have been missed had bronchoscopy been omitted.

Of particular importance in cases selected for surgical resection is bronchial anatomy. Information derived from bronchography is not complete and direct inspection is necessary. The relationship of the upper lobe orifice to the trachea and the relationship of the right middle lobe orifice to the dorsal bronchus of the lower lobe are two important aspects of surgical anatomy made by bronchoscopic inspection.

Since we feel that bronchiectasis is a disease which results from

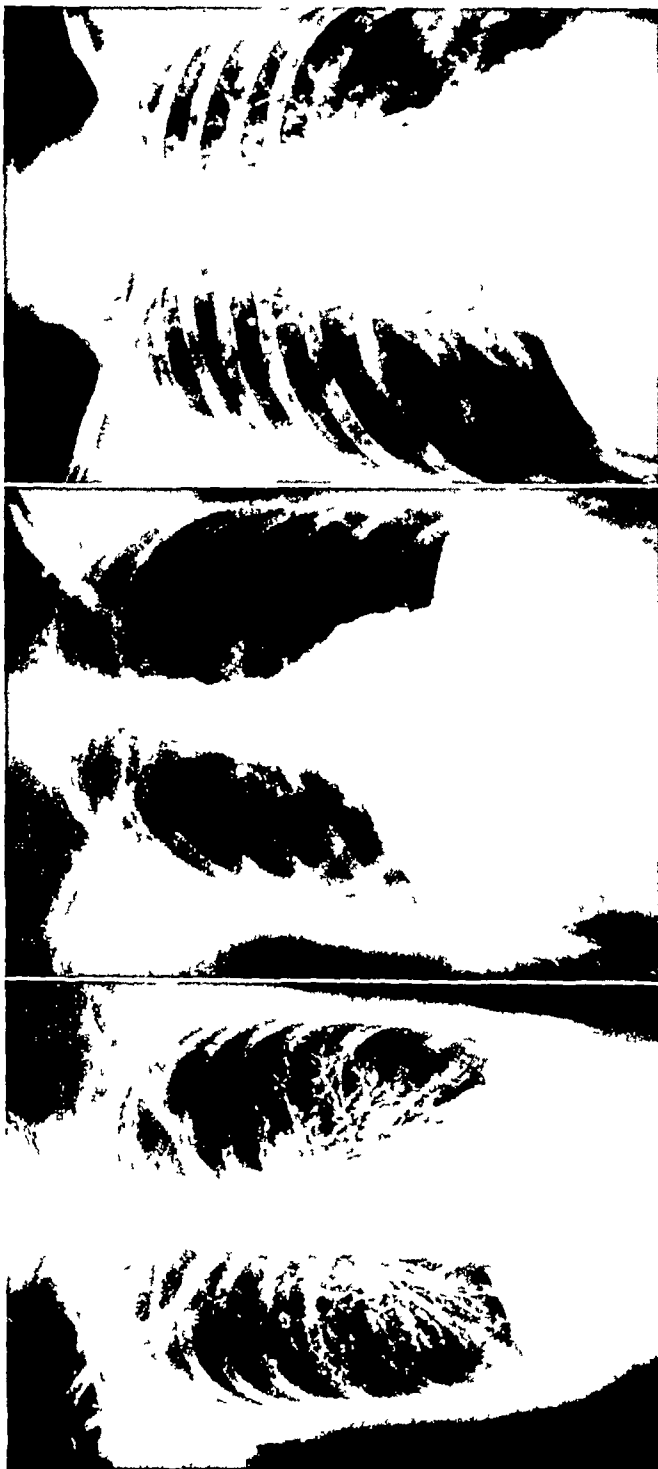


FIGURE 1

FIGURE 2

FIGURE 3

Fig 1 A 36-year-old white female with advanced bronchiectasis of the right middle and lower lobes and the left lingular and lower lobes. The disease was equally distributed by x-ray and physical findings, yet bronchoscopy revealed the right side to harbor the most active infection. A right middle and lower lobectomy was performed with marked relief of symptoms. Resection of the disease on the left has been delayed because of many factors—*Fig 2* A 40-year-old white female admitted in July 1947, with a history of having aspirated a piece of nut shell in 1938. She had cough and malodorous expectoration ever since. The films reveal a small, contracted right lower lobe. Bronchoscopy revealed a foreign body in the orifice of the right lower lobe, and after extraction, it proved to be a large piece of nut shell. After nine years the finding of the foreign body was unexpected. The patient will need a lobectomy because of the irreversible changes in this lobe—*Fig 3* A 65-year-old white male with a four-year history of cough, hemoptyses, and profuse foul sputum. The x-ray film shows characteristic changes of advanced bronchiectasis and pneumonitis. Bronchoscopy revealed an extensive bronchogenic carcinoma almost totally occluding the left main stem bronchus, flush with the carina.

bronchial stenosis and infection, the bronchoscope is necessary in order to rule out or relieve bronchial stenosis, whatever its cause may be. Among these causes are retained secretions as seen in the new-born or following general anesthesia, or inflammatory processes in the lung and bronchi, or foreign bodies, tumors, granulomas, and strictures, or compression stenoses from extrabronchial causes. Of course, in the majority of cases coming to bronchoscopy, the bronchial stenosis no longer exists.

The bronchoscope is also valuable in obtaining secretions for direct smears and cultures uncontaminated by pharyngeal and mouth bacteria. These specimens should be studied both aerobically and anaerobically for bacterial types and fungi. We have found tubercle bacilli on smears in patients in whom a diagnosis of tuberculosis could not be made otherwise. The cultures are useful for the preparation of autogenous vaccines and for determining bacterial type and resistance behavior, so that the most suitable drug may be employed. It seems logical to us that the necrotizing toxin of certain strains of staphylococci must play an important role in the production of this disease.

Finally, the bronchoscope may be useful in determining the lobar source of hemorrhage, and for making iodized oil bronchograms in certain areas which could not be filled and demonstrated by routine methods.

Bronchoscopy in Treatment

In general, bronchoscopic intervention plays an important role in the treatment of bronchiectasis in three types of cases: (1) patients with acute exacerbations of old, usually quiescent bronchiectasis, (2) patients whose disease is anatomically suitable for operation but whose poor general condition precludes operation until the infection has been brought under control and their general condition improved, and (3) patients with a hopeless bronchiectasis, such as those who are too old, or those who have other serious diseases, or those in whom the extent of the involvement contraindicates operation. In these patients bronchoscopy is then employed as a palliative procedure.

The most useful therapeutic purpose of the bronchoscope rests in the ability to aspirate bronchial secretions and to relieve bronchial obstruction. The objective and subjective relief afforded by bronchoscopic aspiration defies adequate explanation in patients who do not have a real bronchial block. It seems unlikely that a patient whose sputum is profuse and is particularly influenced by posture would gain relief for as much as several weeks from such an aspiration, but many case histories will bear out proof of this by the spontaneous return visits of these patients.

requesting bronchoscopies. This relief is no doubt brought about by the violent coughing induced by the bronchoscope which causes a much more thorough expulsion of bronchial secretions than would ever be obtained voluntarily. It is easy to understand the relief afforded by release of an acute inflammatory (mucosal edema or granulation tissue) obstruction with a removal of tenacious secretions from the depths of the smaller bronchi. The actual bronchoscopic technique involves the passage of an appropriate aspirating tip, olive-tipped bougies or small bronchoscopic sponges on a carrier. Following such manipulation, the use of expectorants, inhalations, and postural drainage should be employed.

The value of the bronchoscope in permitting the application of drugs to the mucous membrane has been minimized by some and overemphasized by others. Epinephrine and other sympatheticomimetic drugs applied to a swollen membrane do have some shrinking effect, although much less so than when applied to the nasal mucosa. This action is obviously advantageous in enlarging the bronchial airway. The shrinking agent can be applied on a bronchoscopic sponge or it can be flushed into the bronchial tree directly through the bronchoscope.

The advent of the chemotherapeutic and antibiotic agents brought a brief flurry of hope that topical application through the bronchoscope would be effective. However, we now feel that our hopes were unfounded, for no demonstrable improvement was obtained, probably because of the brief period of contact of the drug. The action of the ciliated epithelium and the cough associated with bronchoscopy soon rid the bronchi of either powder or solution. The aerosol method of inhalation of antibiotics is more sound and has given better results.

Bronchoscopy is not without hazards. Occasionally a severe pulmonary hemorrhage will occur during bronchoscopy. In this event the examination should be terminated, for in our experience bleeding has ceased spontaneously after the withdrawal of the bronchoscope. Of course, a blood transfusion should be given if necessary. An additional hazard is the occasional case of spontaneous pneumothorax which may occur. Sudden chest pain and dyspnoea should make one suspect this complication.

Bronchoscopy in Prophylaxis

A discussion of bronchoscopy in the treatment of bronchiectasis must emphasize the prophylactic treatment. It is a most uncommon pulmonary infection that does not produce some secretion. This secretion is always a potential hazard because if not evacuated promptly, it will occlude the airway. Such occlusion

results in atelectasis, and however transient and however small the bronchus, irreparable damage may occur. It takes a very brief time for the combination of infection and obstruction to destroy bronchial walls, or necrotize pulmonary tissue. Opinion today favors this etiology of bronchiectasis, particularly in children. Therefore, it is urged that all cases with pneumonia, tuberculosis, tracheobronchitis, pulmonary suppuration, or any of the rarer infections be bronchoscoped without delay when the clinical course, physical findings, or roentgenographic details point to retained bronchial secretions. The masking effect of the sulfonamides and antibiotics on pulmonary infections is well recognized and should not be overlooked.

Of particular value in the technique of bronchoscopy in such a case is the use of bronchial lavage in the diseased lobe. An adrenalin solution or a solution of normal saline flushed into such a lobe will initiate coughing, which will usually result in the evacuation of secretions not visible through the bronchoscope.

The bronchoscopist can do much in his own hospital by instructing the residents, anesthetists, and nurses on the importance of (1) not depressing the cough reflex by large doses of morphia or codeine, (2) aspiration of the trachea after general anesthesia when indicated, and resorting to the inhalation of a carbon dioxide-oxygen mixture, (3) frequent turning of the patient after anesthesia and getting him up as soon as possible, (4) using postural drainage properly, (5) the value of aerosol therapy, (6) being on guard for the masking effect of the sulfonamides and antibiotics, and (7) the employment of bronchoscopy early in persistent atelectasis, particularly when infection is present.

SUMMARY

Although bronchoscopy is playing a diminishing role in bronchiectasis, its many uses in diagnosis, treatment, and particularly prophylaxis are so necessary and important that we feel that it should be employed in all cases—as a routine examination—in order to make a more exact diagnosis, as a method of treatment in selected cases, and finally as a most important and valuable prophylactic procedure.

RESUMEN

Aunque se está empleando menos la broncoscopia en la bronquiectasia, sus muchos usos en el diagnóstico, el tratamiento y, particularmente, la profilaxia son tan necesarios e importantes que opinamos que se debe emplear en todos los casos—como examen de rutina—a fin de hacer un diagnóstico más exacto, como tratamiento en casos seleccionados y, finalmente, como procedimiento profiláctico importante y valioso.

Tomography of Larynx in Disseminated Pulmonary Tuberculosis

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Since Dr Felix Leborgne of Montevideo, in 1936, introduced tomography for the diagnostic study of carcinoma of the larynx, this procedure has become definitely established in the diagnosis of this condition. Some years before him, in 1923, Dr Henry Courtard had emphasized the importance of a radiographic examination of this organ.

I have had opportunity to undertake tomographical studies in patients with advanced pulmonary tuberculosis who also had laryngeal manifestations visible on simple inspection. I have studied 10 cases of this nature and have found that it is possible to demonstrate with tomography changes caused by the disease, whether they are in the form of a simple inflammation or other types of specific damage. In almost all of the patients there has been agreement between tomographic findings and those noted on standard laryngoscopic examination.

As a note of technical character we are able to point out the following as for the lateral radiography, imprescendible to perform it for the due study, as for the tomography.

Technique

1) For Lateral Radiography of the Larynx

200 milli Amperes
1/20 second or 10 milli Amper seconds
55 kilo volts for 10 to 13 cm of neck thickness
160 cm distance
Rotating anode tube
Focusing on the thyroid prominence
Vocalization in "U"

2) For Tomography

20 milli Amperes
3 seconds or 60 milli Amper seconds
75 kilo volts or less
Focusing on the thyroid prominence
Vocalization in "U"
Rotating anode tube



FIGURE 1

Figure 1 I D Bilateral extensive caseous tuberculosis with third degree dissemination on both sides Occlusion of both ventricles Laryngoscopic diagnosis Polypoid granulation right vocal cord —*Figure 2 B C* Bilateral extensive caseous tuberculosis with 3rd grade dissemination Occlusion of the left ventricle Laryngoscopic diagnosis Arytenoidal infiltration (left) and Paresis of the respective vocal cords —*Figure 3 W G* Bilateral extensive caseous tuberculosis disseminated Occlusion of both ventricles with impossibility to recognize their outline or the vocal cords Laryngoscopic diagnosis Tuberculous laryngitis infiltrative-edematous form

FIGURE 2

FIGURE 3

FIGURE 4

Figure 4 M J B Bilateral extensive caseous tuberculosis with 3rd grade dissemination Occlusion of both ventricles with impossibility to recognize their outline or the vocal cords

It is necessary to emphasize the following facts Dr Leborgne in his book "Cancer of the Larynx," recommends that the films be taken with the patient in the supine position In this position it has not been possible for us to get satisfactory films On the other hand, placing the patient in the prone position, excellent results have been possible as can be seen in the illustrations

A constant tomographic sign in all cases is the subglottic angle, which, as a rule, is rectangular, becomes frankly obtuse, regardless of the degree of tuberculous laryngitis (cases 2 and 3, arrows)

SUMMARY

This preliminary communication has been written with the purpose of calling attention to a diagnostic approach Conclusions as to the clinical value of this method will be reported as soon as observations are gathered on a larger number of patients

RESUMEN

Se ha escrito esta comunicacion preliminar con el propósito de llamar la atencion sobre un método diagnostico Se publicaran conclusiones sobre el valor clinico de este método tan pronto como se acopien observaciones en un numero mayor de pacientes

A Case of Fatal Tularemic Pneumonia with Necropsy*

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The following case of tularemic pneumonia, with necropsy findings, is presented to demonstrate that earlier awareness of such a diagnostic possibility might well have resulted in the patient's recovery. *P. tularensis* should always be considered a possible etiologic agent in severe primary atypical pneumonia.

According to the United States Public Health Service, the yearly reported incidence of tularemia in the United States has varied between 960 and 2291 for the ten year period from 1937 through 1947, with a mortality of about 5 per cent.

Clinically, tularemia has been classified as ulcero-glandular, oculo-glandular, and typhoidal. In the typhoidal type there is neither demonstrable primary lesion of skin or eye, nor superficial lymph node enlargement. Of 1856 cases reported by Francis,¹ 119 or 6.4 per cent were typhoidal.

Pulmonary and pleural involvement occur in all three varieties of tularemia, but predominate in the typhoidal. Of Foshay's² 554 cases of ulcero-glandular and oculo-glandular tularemia, approximately 15 per cent had evidence of pneumonia as contrasted with 52 per cent of his 46 typhoidal cases.

In a recent review of cases of tularemic pneumonia, reported in the American literature, Stuart and Pullen³ could only collect 253, to which they added 15 of their own. Of these 268 cases, 97 or 36.2 per cent conformed to the typhoidal type of infection. Hunt⁴ has added 12 and Morgan⁵ 15, making a total of 295 cases of pulmonary tularemia reported to date. A diagnosis of pneumonia, primary, atypical, etiology unknown, has probably masked others.

Blackford and Casey,⁶ writing before the introduction of streptomycin, reported the mortality in tularemic pneumonia to be approximately 30 per cent. Hunt⁴ and Morgan⁵ had but one death in 27 cases treated with streptomycin. Once pulmonary involvement occurs, tularemia becomes a real threat to life in the absence of prompt and adequate streptomycin therapy.

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Report of Case with Necropsy

A 48 year old, white, male insurance salesman, a resident of Lansdale, Pa., was admitted to Hahnemann Hospital at 8 45 P M on November 13, 1947

Because of the patient's stuporous condition, the history was obtained from his wife The patient had felt well until November 2, 1947, when he had a distinct chill, with sudden onset of severe frontal headache, fever, and dyspnea Vomiting occurred on November 4th By November 11th severe cough was present, and blood-tinged sputum was noted the next day Dyspnea and fever of 100 to 103 degrees F were prominent and persistent throughout the illness, the dyspnea becoming severe by November 11th

He was treated by two physicians at home before hospitalization was advised, and had received a sulfonamide (type and dosage unknown) and approximately 2,500,000 units of penicillin White counts taken on November 11th and 13th were 7,200 and 4,500 respectively, with an essentially normal differential count The Widal test was negative

At the time of admission to the hospital, the patient appeared critically ill, dehydrated, and was unable to answer questions The temperature was 102.8 degrees F, pulse 120, and respirations 56 per minute, abdominal in character The blood pressure was 134/78 Fine, medium, and coarse rales were heard from the apex to base of both lungs The percussion note over the left lower lobe was flat, and the right lower lobe was dull on percussion Examination of the abdomen was unsatisfactory because of marked rigidity Bilateral ankle clonus was present In other respects physical examination was not remarkable

The blood count showed 10.3 grams of hemoglobin, 3,640,000 red cells,



FIGURE 1 See Text

and 4,600 white cells, non-segmented polys 10 per cent, segmented polys 74 per cent, lymphocytes 15 per cent, monocytes 1 per cent The spinal fluid examination showed normal manometrics, and had a normal cell count, chloride, protein and sugar content The blood and spinal fluid Wassermann test were negative Agglutination tests for typhoid, paratyphoid, rickettsia and brucella abortus were negative, as were cultures of the throat, spinal fluid and blood Examination of the sputum failed to reveal tubercle bacilli, and a culture showed a few colonies of *B pyocyaneus* and pneumococci The feces were negative for ova and parasites Urinalysis was normal The icterus index was 33.3

X-ray films of the lungs revealed a patchy pneumonia involving the lower two-thirds of both lung fields, confluent at the bases, and worse on the left side (Fig. 1)

Although adequate supportive treatment was instituted in the form of oxygen inhalations and intravenous fluids, the patient's condition in the hospital steadily deteriorated On admission full dosage of penicillin and sulfadiazine was begun, and on the second day streptomycin was given, 0.5 grams every 6 hours Stupor deepened incontinence of urine and feces developed, and jaundice became evident The patient died at 4:45 P. M. on November 15th, 56 hours after admission

The clinical diagnosis was pneumonia primary, atypical, etiology unknown Viral pneumonia of known etiology (influenza, psittacosis, lym-



FIGURE 2 Low Power View of Necrotizing Pneumonia Note the partially necrotic exudate filling the alveoli the thickened alveolar walls due to edema endothelial swelling, cellular infiltration and septal cell proliferation

phogranuloma venereum, lymphocytic choriomeningitis) was considered a possibility, while typhoidal tularemia with pneumonia was ignored

The pertinent findings at the postmortem examination by Dr John E Gregory follow The skin and superficial lymph nodes were normal Both pleural sacs were obliterated by dense adhesions The tracheo-bronchial tree was filled with dark, brownish mucoid secretion, following the removal of which there was seen a reddened, hemorrhagic mucosa The lower lobes of both lungs were the site of a confluent lobular pneumonia, which on microscopic examination showed a necrotizing inflammatory reaction (Fig 2 and 3) The spleen was eight times it's normal size Focal necrosis was demonstrated in the liver, spleen, kidneys and bone marrow An agglutination test of heart blood for *P tularensis* was negative, and cultures of heart blood were sterile A guinea pig inoculated with bronchial secretion died shortly after inoculation, and too soon for the development of lesions Giemsa stained lung sections showed several clusters of very small coccoid bacilli that could well have been *P tularensis* Permission to examine the brain was not granted

The gross findings were such that further inquiry from the wife disclosed for the first time the vital information that the deceased had been hunting rabbits on November 1st, and had skinned two rabbits on the same day, 17 hours before the onset of symptoms In view of the history, the necrotizing lesions, and the demonstration of small coccoid bacilli in the lung sections, there seems little doubt that this is a case of tularemia of the typhoidal type with pneumonia

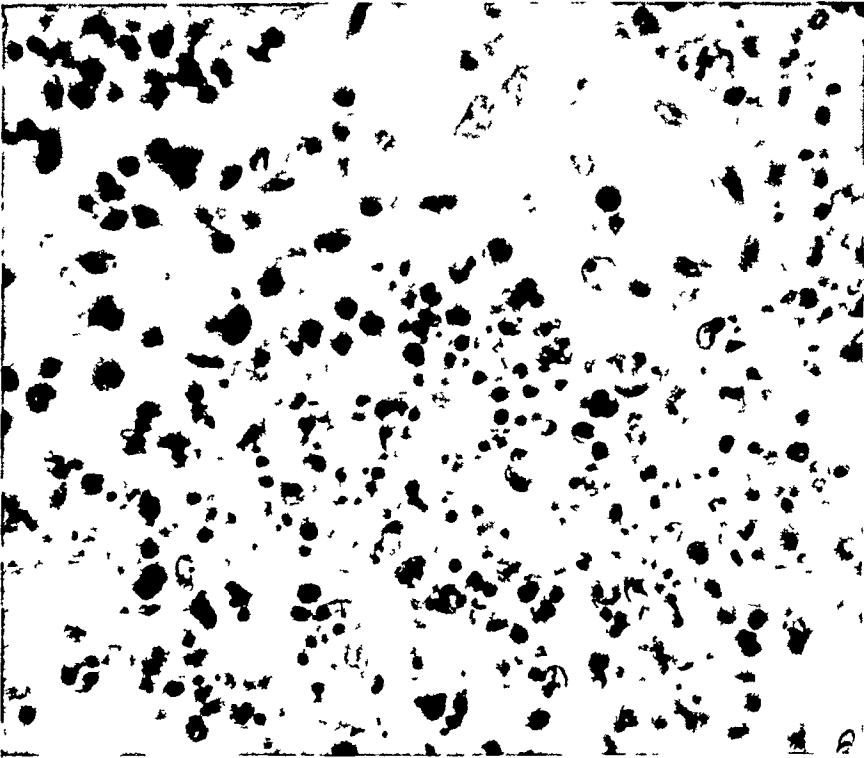


FIGURE 3 High Power of Same Field This shows the character of the exudate and of the alveolar wall changes in detail

Comment

Our unfortunate experience in this case has caused us to examine critically our current methods used in searching for the possible causative agents in severe cases of primary atypical pneumonia. It is well known that the isolation of *P. tularensis* is difficult, requiring special culture media such as dextrose-cystine-blood agar⁷ and hazardous animal inoculation. Nevertheless, these procedures offer the only means of early diagnosis in typhoidal tularemia, since, as in this case, agglutination tests for *P. tularensis* are negative until the end of the second to fourth week of the disease. Lung puncture should be considered in the absence of sputum.

If typhoidal tularemia is recognized as a diagnostic possibility, a history of exposure to wild rabbits or ticks will often be obtained.

It would seem to us safest, as has been recommended by Hunt⁴ and Morgan,⁵ to give streptomycin a therapeutic trial in hospitalized cases of severe atypical pneumonia, while every available means is being used to establish an etiologic diagnosis.

Had direct inquiry been made about exposure to wild rabbits, had more careful bacteriologic investigation been made, and had streptomycin been administered earlier, the outcome in the case described might well have been favorable.

SUMMARY

1) About 6 per cent of tularemia are typhoidal, and probably half of these have pulmonary involvement.

2) A case of tularemic pneumonia, diagnosed at autopsy, is described.

3) Early inquiry as to possible wild rabbit or tick contacts should be made in all cases of primary atypical pneumonia.

4) In severe cases of primary atypical pneumonia special laboratory techniques should be used in an attempt to demonstrate *P. tularensis*, since agglutination tests may remain negative until the fourth week of the disease.

5) In such severe cases a trial of streptomycin is suggested while search for an etiologic agent is in process.

RESUMEN

1) Aproximadamente el 6 por ciento de los casos de tularemia son de tipo tifoideo y probablemente la mitad de ellos tienen lesiones pulmonares.

2) Se describe un caso de neumonía tularémica diagnosticada por la autopsia.

3) En todo caso de neumonía atípica primaria se debe inves-

tigar prontamente la posibilidad del contacto con conejos salvajes o garrapatas

4) En casos graves de neumonía atípica primaria deben emplearse técnicas especiales de laboratorio para tratar de demostrar la P tularense, pues las pruebas de aglutinación pueden continuar negativas hasta la cuarta semana de la enfermedad

5) Se sugiere que se ensaye la estreptomycin en esos casos graves, mientras se prosigue la busca del agente etiológico

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Bronchographic Observations in Collapsed Lungs*

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General Considerations The similarity between the phenomena that govern pulmonary ventilation and the entrance of lipiodol from the trachea to the alveolus, has made us think that it may be possible to record bronchographically some of the changes caused by the collapse of the lung. In fact, the lungs may be ventilated when their bronchi are patent and their thoraco-alveolar system is unchanged, likewise, the opaque material fills the major bronchi when they are patent, and the alveolus only when it is aspirated on inspiration. Stating the question in this manner, we shall not pretend to draw conclusions, but from the accompanying bronchograms we shall make some deductions whose validity we leave to the reader.

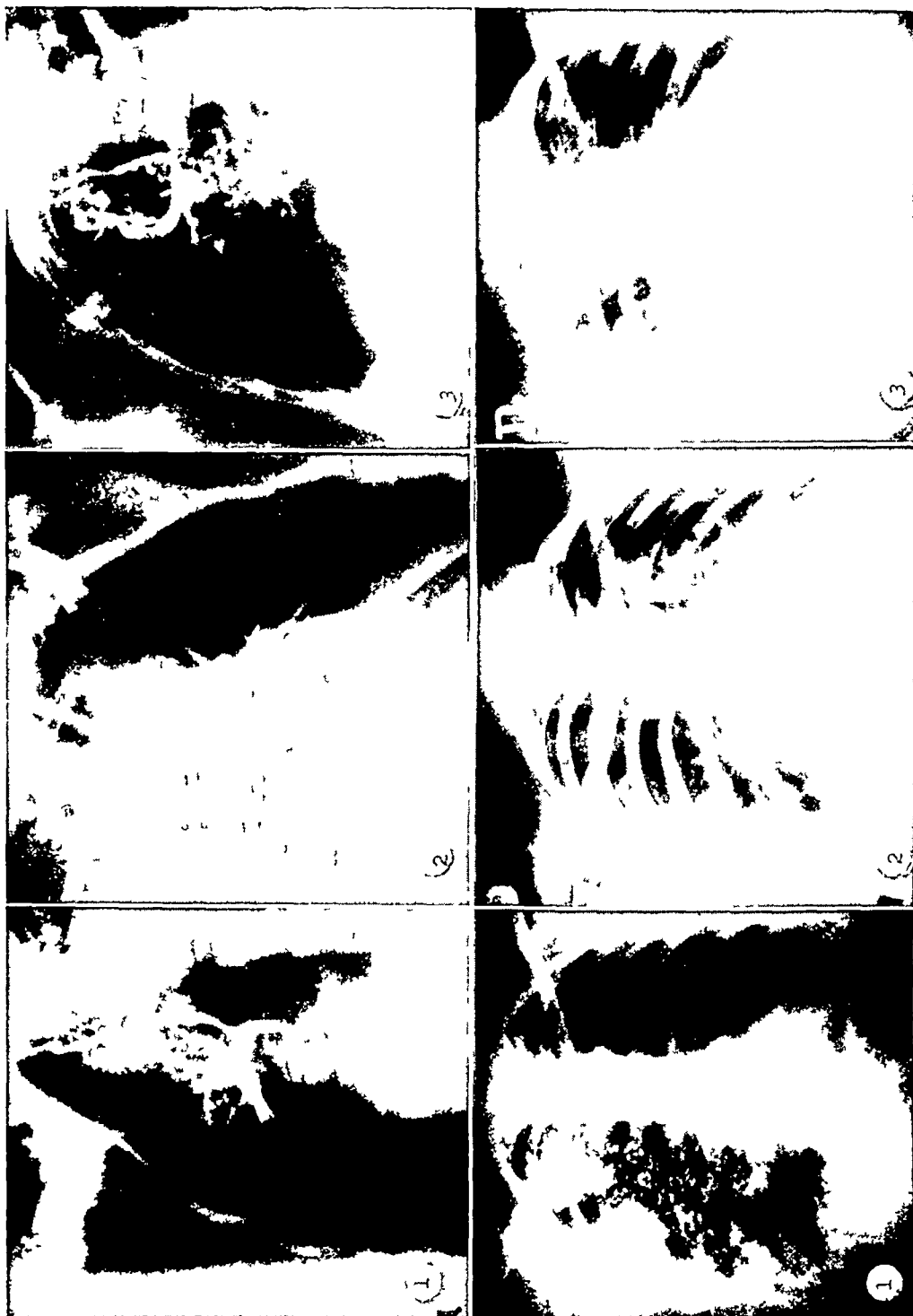
The work of S. Di Rienzo, "Radiological Exploration of the Bronchus," has served us as the fundamental basis for this study and, in addition, we have had the excellent collaboration of the radiologist Dr. Vicente Ubillus.

Bronchographic Observations Bronchograms 1 and 2 represent normal bronchograms. Note the filling of the major bronchi of the upper lobe of the right lung and the beginning of the foliage-like alveolar filling (Fig. 1). In the film taken 10 minutes later (Fig. 2) one sees that the canalicular phase has ended and the lipiodol is found in the alveoli, appearing as masses of greater or lesser density caused by the superimposition of shadows.

Bronchograms 3 and 4 Female patient treated with left pneumothorax for eight months. Note the filling of the major bronchi of the entire left lung, the absence of secondary branches and of "foliage," in spite of having kept the patient in an adequate position for 10 minutes (Fig. 3). The film taken 15 minutes later (Fig. 4) shows the abnormal persistence of the canalicular phase, the absence of "foliage," the displacement of the major bronchial branches and the air space produced by the artificial pneumothorax.

Bronchograms 5 and 6 Female patient who had a right phrenic exeresis and has been under treatment for one year. Note that in this case the secondary bronchial branches and the "foliage"

*Presented at a scientific session, November 7, 1946.



are absent in the upper lobe, the major branches are filled with opaque substance but are dilated into small sacs (Fig 5) Fluoroscopically, it was possible to demonstrate a marked change in bronchial dynamics and tonicity In Figure 6 one may see the elevated right hemidiaphragm and the formation of "foliage" in relation with the anterior branches of the lower lobe—this was confirmed in a lateral film

DEDUCTIONS

1) It is evident that pulmonary collapse brings about a state of hypoventilation in the collapsed lung, due to changes in bronchial patency and in the respiratory function of the thoraco-alveolar system These changes, demonstrable by bronchography, would be manifested in spasms and partial or total bronchial obstructions with their immediate consequences, alveolar emphysema or atelectasis, which may affect from small areas to an entire lung

2) Phrenic exeresis produces an effect similar to artificial pneumothorax, especially in the upper lobe and the posterior part of the lower lobe, but, in addition, it causes dilatation of the major bronchi due to relaxation of their muscular layers

DEDUCCIONES

1) Es evidente que el colapso pulmonar origina un estado de hypoventilación en el pulmón colapsado, mediante alteraciones en la permeabilidad bronquial y el funcionamiento aspirativo del sistema tóraco-alveolar Estas alteraciones demostrables con la broncografía, se manifestarían mediante espasmos, obstrucciones parciales o totales de bronquios con sus consecuencias inmediatas: insuflaciones alveolares o atelectasia que pueden afectar desde pequeñas zonas hasta la totalidad de un pulmón

2) La frénico-exéresis produciría acciones semejantes al neumotórax artificial, especialmente en el lóbulo superior y parte posterior del lóbulo inferior, pero además se producirían dilataciones de los bronquios principales por relajamiento de sus capas musculares

FIGURE 1 (Top) Normal bronchogram Initial (Canalicular) phase (Bottom) Normal bronchogram Formation of Foliage After 10 minutes—FIGURE 2 (Top) Bronchogram with Pneumothorax Canalicular phase (Bottom) Bronchogram with Pneumothorax Absence of Foliage Persistence of the canalicular phase after 20 minutes—FIGURE 3 (Top) Bronchogram with Phrenicectomy Canalicular phase (Bottom) Bronchogram with Phrenicectomy After 20 min

A Brief Analysis of Fifty Foreign Bodies in the Larynx, Trachea and Bronchi*

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The special methods of diagnosis and treatment applied in the present series of foreign bodies located in the larynx, trachea and bronchi are similar to the methods I have learned from my esteemed teachers, Professors Chevalier Jackson and Chevalier L Jackson Therefore, my statistical observations cannot but be a humble addition to those extensively charted, developed and described by them in 1945 At that time they had analyzed 3,122 cases of foreign bodies in the upper food and lower air passages of a total numbered collection of 4,259 to which I had the great privilege of contributing in a small way when I had the good fortune to be their assistant more than ten years ago At present, I have a collection of 285 specimens of foreign bodies of which 80 were removed from the lower respiratory passages during the past 9 years All the others were found in the upper food passages

The present statistics deal with the first series, fully charted, of 218 foreign bodies Speaking of this series, 22 per cent or 50 were found in the lower respiratory track Of these 50, 4 were located in the larynx (8 per cent), 4 in the trachea (8 per cent), 42 in the bronchi or 84 per cent of the grand total of inhaled foreign bodies That is to say that when a foreign body was inhaled, in 85 per cent of the cases it was aspirated into a bronchus, and two times out of three into a right bronchus

The nature of the foreign bodies was rather varied 22 peanuts or 44 per cent of the total, 10 other vegetable or organic bodies (20 per cent), 16 metallic bodies (32 per cent) Forty-four of these patients were children (88 per cent), 6 only were adults (12 per cent) This difference can be explained by the tendency on the part of children to bring every object to the mouth and to place small objects in the mouth One of our women had inhaled her foreign body 14 years previously, during her childhood The patient's ages extended from 8 months to 46 years but were mostly between 1 and 3 years, apparently an age period when children are inexpert at eating and especially at chewing peanuts Recovery

*From the Department of Broncho-Esophagology, Ste-Justine Hospital, Montreal, Canada Presented on the International Night Program, 13th Annual Meeting, American College of Chest Physicians, Atlantic City, New Jersey, June 5, 1947

was complete except in three cases. These three patients were in such poor condition when they were brought to us that recovery could not be expected. These three patients were the only ones who required tracheotomy to permit the greatest freedom of manipulation and the greatest possibility of survival.

We have been able to observe every possible degree of bronchial obstruction, complete or incomplete brought about by the presence of these foreign bodies, as well as the secondary suppuration, emphysema and obstructive atelectasis. In about ten of these patients there was no history of a foreign body, in several of these and in a few others radiological examination was negative or showed very little to suggest a foreign body as a possible causal agent. The others mentioned vaguely that choking had occurred after placing a foreign body in the mouth. Only half of the patients sought or were brought for treatment during the first twelve days following the accident. At least 25 were admitted to hospital after a period varying from 12 days to 14 years after the entrance of the foreign body into the airways, in most cases the delay was caused by delay in diagnosis.

The nature of the foreign bodies has been varied enough.

I Thirty vegetable or organic bodies (60 per cent of the total) of which 22 were peanuts (44 per cent of the total) the remains of a large dried bean, a timothy top, a fragment of a nut shell, two fragments of bone, two teeth, a chip of wood, a segment of pericarp of apple.

II Sixteen metallic bodies or 32 per cent of the total. 4 open safety pins (plain and fancy), 2 common pins, 1 metal eraser holder from a pencil, the tubular portion of a tracheotomy cannula, the shell of a 22 rifle bullet, a part of a screw, the flexible part of a suction apparatus, a triangular piece of sheet iron, a $\frac{3}{4}$ inch nail, 2 carpet tacks, the shell of a fuse, the tab of a zipper.

III Other foreign bodies. An oval wooden bead from a rosary, a large glass bead from a necklace, a piece of Celluloid from a toy.

According to Jackson 99 per cent of peanuts are removed from children. In that series I also have found only one peanut in an adult, a woman of 46 years. If one excepts this patient the ages extend from 15 months to 10 years, and are mostly between 1 and 3 years. These two years furnish our largest contingent for this type of foreign body, that is 77 per cent of all peanut cases, namely 17 out of 22.

INHALED PEANUTS

Length of Sojourn 4 months in the adult, 2 days to 2 months in the children.

<i>No</i>	<i>Name</i>	<i>Age</i>	<i>Foreign Body</i>	<i>Location</i>	<i>Length of Sojourn</i>	<i>Main Symptoms</i>
51	Noel M	19 months	4 fragments of a dried bean	Trachea, right and left bronchi	3 weeks	Fever, stridor, indrawing, cyanosis
52	Francoise D	22 months	Segment of pericarp of apple	Larynx	2 months	Laryngeal stridor, indrawing, dyspnea, aphonia
53	Denis G	20 months	Timothy top with spike	Left lower lobe bronchus	3 months	Juicy cough, fetid breath
54	Marcel L	8 years	Fragment of a hazel nut shell	Right lower lobe bronchus	6 months	Spiking fever, cough, septicemia, bad general condition
55	Mrs Aime P	35 years	Fragment of beef bone	Left lower lobe bronchus	15 days	Painful cough, distress, fever
56	Claude L	2 years	Chip of wood	Left lower lobe bronchus		Cough
57	Unice S	7 years	Molar tooth	Right main bronchus	3 weeks	Cough, fever, dyspnea
58	Mrs John C	43 years	Chicken bone (small vertebra of neck)	Right main bronchus	10 days	Spells of painful coughing, acute pain in right chest, fetid breath
59	Marthe P	7 years	Incisive tooth	Right main bronchus	18 days	Cough and fever Signs of atelectasis at right base

SIXTEEN METALLIC FOREIGN BODIES

8 on right side
7 on left side

50 per cent
43 per cent

60	Real M	6 years	Metal eraser holder from a pencil	Left lower lobe bronchus	5 days	Slight cough only
61	Dieudonne B	36 years	Tubular portion of a tracheotomy cannula	Right main bronchus	10 days	Cough only
62	Leonce L	5 years	Shell of a 22 rifle bullet	Left inferior lobe bronchus	17 days	Spells of cough and choking
63	Rolland L	13 years	Open large collar pin	Larynx and trachea	24 hours	Cough and dyspnea
64	Yvette V	3 years	Part of a screw	Right lower lobe bronchus	21 days	Indrawing, spiking fever, exhaustion, critical condition

<i>No</i>	<i>Name</i>	<i>Age</i>	<i>Foreign Body</i>	<i>Location</i>	<i>Length of Sojourn</i>	<i>Main Symptoms</i>
65	Lucien F	33 years	Flexible part of a suction apparatus	Bronchus of posterior segment of right upper lobe	2 days	Access case of right upper lobe
66	Annette T	21 years	Common pin	Right lower lobe bronchus	4 days	Cough, blood spitting
67	Mrs Gerard L	34 years	Small open safety pin with calcium and phosphate deposits	Right lower lobe bronchus	10 years	Productive cough, hemoptysis Frequent attacks of grippe
68	Marcel B	11 years	1 common pin with piece of cork	Trachea	2 days	Slight cough only
69	Mrs Paul B	21 years	Open small collar pin	Left lower lobe bronchus	14 years	Productive cough, many ounces of pus per 24 hours, septic condition Complete carnicification and massive bronchiectasis of left lower lobe
70	Roland M	2 years	Triangular piece of sheet iron	Larynx	12 months	Very marked dyspnea, indrawing and cyanosis Critical condition
71	Jacqueline C	3 years	$\frac{3}{4}$ inch nail	Left main bronchus		Intermittent cough
72	Jean-Guy D	21 months	2 carpet tacks	Right main bronchus	48 hours	Dyspnea, wheezing, cough and distress Fever
73	Jacques B	8 months	Open fancy stick pin	Larynx and trachea	24 hours	Dyspnea, indrawing, aphonia, cyanosis
74	Jacqueline R	5 years	Shell of a fuse	Right main bronchus	1 week	Slight cough only
75	Jacqueline B	6 years	Tab of a zipper	Right main bronchus	1 week	Cough

OTHER MISCELLANEOUS FOREIGN BODIES

76	Aline D	10 years	Piece of celluloid from a toy	Larynx	24 hours	Marked stridor, indrawing and dyspnea Aphonia
77	Claude M	2 years	Oval wooden bead from a rosary	Right main bronchus	24 hours	Signs of obstructive emphysema of left lung Slight wheezing
78	Yves I	4 years	Large glass bead from a necklace	Left main bronchus	18 hours	Signs of obstructive emphysema of left lung slight wheezing

Location 10 in the right main bronchus (45 per cent), 4 in the left main bronchus (19 per cent), 2 in the right inferior lobe bronchus (9 per cent), 2 in the left inferior lobe bronchus (9 per cent), 3 in the trachea (13 per cent), 1 in the left superior lobe bronchus

Clinical Signs in Children Asthmatoïd breathing, rhonchi and obstructive emphysema in most of the patients, indrawing of the chest, dyspnoea, cyanosis in 3 patients

Radiological Findings In about 50 per cent of the cases of peanuts, during expiration, emphysema of the obstructed lung, but there was displacement of the mediastinum towards the non-obstructed side, in a few cases only, atelectasis of the obstructed lobe or lung with displacement of the mediastinum towards this side was noticed in only a small number of children

In a certain number of cases entirely negative findings

In the adult, whom I use for purposes of comparison, and who kept her foreign body for 10 months, there was chronic suppuration which could have passed for a bronchiectasis or tuberculosis. For this reason this patient had been under observation in a provincial sanatorium for several weeks and from there was sent to us for bronchoscopic examination

I shall now outline briefly a few particularly interesting case histories 1) A timothy top was found in the left inferior lobe bronchus in a child of 20 months. Putrid suppuration of the left inferior lobe of 3 months duration cause unknown. The top is complete with a fairly long piece of the spike. This case was reported at length in *Les Annales Médico-Chirurgicales de l'hôpital Sainte-Justine* (1941)

2) A section of the pericarp of an apple was suspended between the vocal cords of a child for 2 months. This child of 22 months showed stridor with inspiration, a croupy cough and dyspnoea simulating the syndrome of infectious or contagious laryngitis

3) Half the shell of a hazelnut was removed from the right inferior lobe bronchus. It had been inhaled 6 months previously. This was a prize discovery for bronchoscopy because the clinical picture was that of a pleurisy with effusion or a pneumonia. It actually was simply a lobar atelectasis from obstruction

4) Removal of 9 metallic foreign bodies, 4 in children

(a) Part of the metallic band of a pencil. A boy of 6 years length of sojourn 5 days in the left bronchus. A little cough only and a few rhonchi

(b) A long safety pin, open, point up, between the vocal cords. Length of sojourn 24 hours. A boy of 13 years. Symptoms cough and dysphonia

(c) The body of a screw lodged in the left bronchus for 21 days Child of 3 years On admission general condition critical, indrawing of the chest, high fever, exhaustion

(d) The shell of a 22 caliber projectile lodged for 12 days in the bronchial tree of a boy of 5 years (Case reported in *Les Annales Médico-Chirurgicales de l'hospital Sainte-Justine*, 1940)

Five foreign bodies in the bronchi in adults

1) Open safety pin, point up, in the left lower lobe bronchus on the left side, in a woman of 21 This pin had been inhaled 14 years previously when the patient was 7 years of age A left pleural empyema had been drained at the age of 11 years, a fistula followed and persisted for 6 months Copious expectoration daily since the fistula closed Signs of putrid suppuration and toxæmia To sum up she looked so much like a toxic case of tuberculosis that the Chest Specialists had forbidden her to nurse her baby and even isolated her from her child

2) A tracheotomy cannula in a man suffering from cancer of the larynx—age 36 years, lodged in the right bronchus for 10 days Transitory purulent bronchitis with localized ulcerations and without signs of obstruction (Reported in the *Transactions of The American Association of Broncho-Oesophagology*, 1941)

3) The end of a metallic suction apparatus in the right superior lobe This patient was 33 years of age and had a pulmonary abscess in this lobe

4) An open safety pin in a woman of 41 years This object had been lodged in the right inferior lobe bronchus for 12 years and was discovered when a radiograph was made on account of hemoptysis (Presented before *La Société de Phtisiologie de Montréal* in 1941 and published in the *American Annals of Oto-rhino-laryngology*)

5) A fragment of beef bone in a workman, 35 years of age, lodged in the left bronchus for 15 days Painful cough, fever, foetid expectoration No abnormal x-ray shadows other than such as to suggest a peri-bronchial reaction at this level

SUMMARY

On the whole we noticed that the symptoms and physical signs produced by foreign bodies could simulate those of bronchopulmonary diseases such as bronchial asthma, bronchopneumonia, tumors, infectious bronchitis and even tuberculosis

It is thus most important that a complete study be made in every case in which the diagnosis of the bronchopulmonary dis-

ease has not been firmly established or confirmed. By a complete study we mean a complete past family and personal history, a careful physical examination, radiological studies, laboratory analyses and bronchoscopic exploration, followed if necessary, by complementary bronchographic studies.

Bronchoscopy, that is the bronchoscopic operation, is the only one that permits the removal of the cause of the obstruction, that is, the foreign body, or that provides the means of enlarging the lumen of a bronchus obstructed by a swollen mucosa, false membranes, debris, shreds of tissue or viscid secretions. It is in this way that the formerly appalling mortality in this type of illness has been reduced to the respectable figure of 2 per cent, 2 to 4 per cent only of foreign bodies in the bronchi are expelled by coughing, about 99 per cent can be removed by peroral bronchoscopy with a resultant complete recovery in 98 per cent of cases even if the prolonged sojourn of the foreign body has brought about extensive pathological changes.

In conclusion, we wish to point out that foreign bodies cause many deaths by asphyxia before the victim can get to a physician.

RESUMEN

En general, se observó que los síntomas y signos físicos producidos por cuerpos extraños pueden imitar los de enfermedades broncopulmonares, tales como asma bronquial, bronconeumonía, tumores, bronquitis infecciosa y aun tuberculosis.

Por consiguiente, es sumamente importante que se lleve a cabo un estudio completo de cada caso en el que no se ha establecido o confirmado firmemente el diagnóstico de la enfermedad broncopulmonar. Por un estudio completo queremos decir una historia completa del pasado de la familia y de la persona, un examen físico cuidadoso, estudios radiográficos, análisis de laboratorio y exploración broncoscópica la que debe ser seguida, si es necesario, de estudios broncográficos complementarios.

La broncoscopia, es decir, la operación broncoscópica, es la única que permite la extracción de la causa de la obstrucción, a saber, el cuerpo extraño, o que ofrece el modo de ensanchar la luz de un bronquio obstruido por una mucosa hinchada, membranas falsas, desechos, fragmentos de tejidos o secreciones viscosas. De esta manera la mortalidad por esta enfermedad, anteriormente aterradora, ha sido reducida a la cifra respetable del 2.2 al 4 por ciento. Solamente un pequeño porcentaje de los cuerpos extraños en los bronquios son expulsados mediante la tos, el 99 por ciento, mas o menos, pueden ser extraídos mediante la broncoscopia oral, con la resultante reposición completa del 98 por ciento de los

casos, aun si la permanencia prolongada del cuerpo extraño ha producido alteraciones patologicas extensas

En conclusión, deseamos indicar que los cuerpos extraños causan muchas muertes por asfixia antes de que la victima pueda llegar donde el doctor

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Fifteenth Annual Meeting American College of Chest Physicians

The American College of Chest Physicians concluded a most successful meeting in Atlantic City, New Jersey, on June 5th. Over 900 doctors and their wives registered for this important meeting. A complete list of the registration is published in this issue. Reports of the activities of the meeting will be published in future issues of "Diseases of the Chest."

The scientific program was of the highest caliber which is a tribute to the Committee on Scientific Program whose members labored diligently in order to make this possible. The X-Ray Conference, conducted by Dr. M. C. Sosman of Boston, was one of the highlights of the meeting. It is unfortunate that more people could not be accommodated at the round table luncheons, most of which were sold out in advance of the opening dates of the meeting. The critical reviews on various aspects of chest diseases were well received and the evening devoted to the presentation of motion pictures drew a large audience.

More than 500 doctors and their wives attended the Annual Presidents' Banquet at which time guests from all of the other countries were introduced. Dr. Irving Willner, Chairman of the Committee on General Arrangements and all of the members of the New Jersey Chapter of the College are to be congratulated upon the excellent arrangements made for the meeting. Mrs. Irving Willner and the other members of the Women's Reception Committee are also to be congratulated for the hospitality extended to the doctors' wives who attended the meeting.

The following officers were elected for the year 1949-1950

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 Philippine Islands Manuel Quisumbing, M D, San Pablo
 Uruguay Armando Sarno, M D, Montevideo
 Northern Italy Attilio Omodei Zorini, M D, Rome
 All present Governors in other countries were re-elected

ANNUAL MEETING REGISTRATION

<i>State</i>	<i>No Registered</i>
Alabama	6
Arizona	3
Arkansas	4
California	28
Colorado	15
Connecticut	9
Delaware	5
District of Columbia	14
Florida	11
Georgia	10
Illinois	55
Indiana	8
Kansas	4
Kentucky	18
Louisiana	5

	No Registered
Maine	4
Maryland	26
Massachusetts	22
Michigan	17
Minnesota	10
Mississippi	2
Missouri	14
Nebraska	3
New Mexico	1
New Jersey	92
New York	196
North Carolina	7
North Dakota	1
Ohio	42
Oklahoma	6
Oregon	3
Pennsylvania	94
Rhode Island	5
South Carolina	5
South Dakota	1
Tennessee	8
Texas	18
Utah	1
Virginia	19
Washington	1
West Virginia	14
Wisconsin	2
TOTAL	<hr/> 809
<i>United States Possessions</i>	
Alaska	1
Hawaii	3
Puerto Rico	7
TOTAL	<hr/> 11
<i>Other Countries</i>	
Argentina	7
Belgium	1
Brazil	1
Canada	44
Chile	4
Cuba	7
England	1
India	1
Mexico	8
Republic of Panama	1
Peru	2
Philippine Islands	2
Portugal	3
South Africa	2
Spain	1
Switzerland	3
Venezuela	1
TOTAL	<hr/> 89
GRAND TOTAL	<hr/> 909

REPORT OF THE TREASURER

Financial Statement, May 31, 1949

The financial condition of the American College of Chest Physicians is more satisfactory than last year. We are not in the red in spite of the fact that expenses have doubled and the journal of the College is now being published twelve times a year instead of six times.

The actual cash income to 12/31/48 totalled \$60,891 23

This amount came from the following items

(1) New membership fees	\$14,405 00
(2) Dues	31,632 00
(3) Sales	
Advertising in Diseases of the Chest	\$7,812 50
Subscriptions	6,314 89
Directory	30 00
Making a total of	14,157 39
(4) Interest on U S Govt Bonds, Series "G"	557 50
(5) Other income	139 34
Making a total of	\$60 891 23

The expenditures were as follows

(1) Salaries	\$20,240 16
(2) Printing Diseases of the Chest	13,852 00
(3) Meeting Expenses	4,635 13
(4) Officers and Committee Expense	2,707 93
(5) Office Rent	4,349 19
(6) Printing and Engraving	1,999 88
(7) Postage and Shipping	2,042 86
(8) Travelling Expense	1,854 65
(9) Sales Discount	1,156 36
(10) Mailing and Posting of journal	1,914 47
(11) Office Expense	1,298 26
(12) Editors Expense, Diseases of the Chest	650 00
(13) Telephone and Telegraph	1,137 02
(14) Secretary to the president	300 00
(15) Secretary to Chairman, Board of Regents	300 00
(16) Membership Certificates	306 54
(17) Advertising Agency Expense	787 15
(18) Auditing	200 00
(19) Annual Award Expense	189 27
(20) Depreciation	361 74
Total Expense	\$60,282 61
Net Income	608 62

We have on reserve in U S Savings Bonds, Series "G" \$33,800 00
of this amount \$3,300 00 has accumulated from life memberships
\$10,500 00 has accumulated for the Research Council
\$20,000 00 has accumulated in the General Fund

I am proud to report to you that the American College of Chest Physicians has gone far to promote the specialty of diseases of the Chest. The College has a very ambitious program and through its councils and committees great progress has resulted.

The American College of Chest Physicians is blessed with dreamers who

have practical dreams The specialty of diseases of the chest is an established fact and it has come about only through the farsightedness and the vision of its officers and members

However, we cannot sit on our laurels and feel happy about our accomplishments A lot of work has yet to be done

Any project that is undertaken by the College requires additional funds Your officers do not desire to tax the members with prohibitive dues There are other ways and means of raising additional funds to take care of our ambitious projects

To do this we must

- (1) Obtain advertisements for Diseases of the Chest and support its advertisers
- (2) Let as many of us as possible, and preferably all of us, obtain life memberships so that more income may accumulate from this fund
- (3) Let us support the Research Council by the raising of funds among our wealthy philanthropic friends
- (4) There are many wealthy patients that leave fortunes when they pass on It may be possible to get any number of them to will a part of their estates to the American College of Chest Physicians or to any one of its special projects
- (5) The College has established a book service department When any of us wish to purchase any book, we can purchase it through our organization so that the publishers' discount may be used by us to a greater advantage

In conclusion I wish to add that the LaSalle Auditing Company of Chicago checked our books and found them in good order

Minas Joannides, M D

REPORT OF THE HISTORIAN

June 1, 1948 - June 1, 1949

Mr President, Fellows of The American College of Chest Physicians and guests

The constant labour and marvelous effort that have been given by physicians from the most distant past to our own time have revealed the truths of medicine as an art and as a science

We pause at this time to pay respect and honour to our fellow physicians who devoted their lives to the application of these truths in the relief of pain and suffering of the afflicted and have now passed to their reward It is fitting and proper that we do this

The names of those Fellows of the American College of Chest Physicians who have passed to their reward since our last meeting are

Dr Lloyd H Patterson, San Fernando, California

Dr Vera Viola Norton, Waverly, Iowa

Dr I R Fox, Eugene, Oregon

Dr Frank R Wheelock, Scranton, Pennsylvania

Dr Eustace T Goff, Vienna, West Virginia

Dr Burton W Rhuberry, Ypsilanti, Michigan

Dr Harry S Newman, Yonkers, New York

- Dr Berthold S Pollak, Jersey City, New Jersey A pioneer worker in the field of tuberculosis in the State of New Jersey A physician in honour of whom the Berthold S Pollak Hospital was named
- Dr Victor Cullen, Baltimore, Maryland A pioneer and leader in tuberculosis work in the State of Maryland President-elect of the National Tuberculosis Association, he stepped aside from the honour of assuming the office of President because of ill health
- Dr Clemente Ferreira, Sao Paulo, Brazil Dean and pioneer worker in the field of tuberculosis in his country
- Dr Robert O Brown, Santa Fe, New Mexico Governor of the American College of Chest Physicians for the State of New Mexico
- Sir Sidney Valentine Sewell, Melbourne, Australia A student and teacher, a physician and a world traveler, possessed of the kindest disposition imaginable which endeared him to all his patients and friends His early studies were in large measure devoted to neurological subjects but later he became interested in the study and treatment of tuberculosis, waging a never ending fight against this scourge He played an important role in presenting to his government the tuberculosis problem and in setting the policy and plans for its eradication in his country The Sir Sidney Sewell Pathological Wing of the New Tuberculosis Sanatorium at Watsonia is a memorial to his constancy and to his unselfish work of love

We pay our respect and do honour to the memory of these departed physicians But, in a larger sense, we pause to rededicate and reconsecrate our efforts, our talents and our lives to the continuation of the never ceasing and unselfish work of charity, love and mercy, begun in the distant past and continued by physicians from time immemorable

The world may little heed what we say, but time nor faulty memory can erase the glorious advances made through their constancy and never-ending search for the truth It is for us to take from these honored physicians of the past an increased devotion to the cause of humanity for which they gave a full measure of devotion, that we shall resolve that their constancy, that their unselfishness and that their labour of love shall not have been in vain, that the welfare of our patients shall always be first in our minds, that the truths of medicine shall blossom forth in a new light and shall remain untrammelled

William A Hudson, M D

POSTGRADUATE COURSE IN BRONCHESOPHAGOLOGY

The University of Illinois, College of Medicine, announces a postgraduate course in Bronchoesophagology which will be supervised by Doctors Paul H Holinger and Albert H Andrews

This course will be held from September 19 to October 1, 1949 For application forms and further information communicate with the Postgraduate Division (Otolaryngology), University of Illinois, 1853 West Polk Street, Chicago 12, Illinois

College Chapter News

ARIZONA CHAPTER

The annual meeting of the Arizona Chapter of the College convened at the Pioneer Hotel in Tucson on May 10, in conjunction with the state medical society meeting. The following officers were elected:

Kent H. Thayer, M.D., Phoenix, President
John W. Stacey, M.D., Tucson, Vice-President
Leslie B. Smith, M.D., Phoenix, Secretary-Treasurer

The President of the Chapter has appointed Dr. Dan Mahoney of Tucson as Chairman of the Medical Education Committee, Dr. John L. Cogland, Chairman, and Drs. N. K. Thomas and Hilton J. McKeown, members of the Program Committee, and Drs. Edward J. Nagoda and Bertram L. Snyder to the Membership Committee.

ARGENTINE CHAPTER

The Argentine Chapter of the College has instituted a postgraduate scholarship at the Catedra de Patologia y Clinica de la Tuberculosis, Buenos Aires for doctors from the interior of the country who are interested in postgraduate training in diseases of the chest. Dr. Raul F. Vaccarezza, Governor of the College, is professor at the institute. Dr. Justo Lopez Bonilla, President of the Argentine Chapter, and Drs. Gumersindo Sayago, Raul Vaccarezza and Agustin Caero constitute the board of examiners. The scholarship pays 400 pesos per month (Arg.) for a period of six months.

ILLINOIS CHAPTER

At the annual meeting of the Illinois Chapter of the College held at the Palmer House, Chicago, on May 15, the following officers were elected:

Darrell H. Trumpe, M.D., Springfield, President
Edwin R. Levine, M.D., Chicago, Vice-President
Charles K. Petter, M.D., Waukegan, Secretary-Treasurer

A resolution was adopted that the chapter go on record as recommending to the state medical society that a Section on Diseases of the Chest be established in the scientific assembly. It was pointed out that the New York State Medical Society and the New Jersey State Medical Society now have such sections.

Plans were discussed for the annual postgraduate course in diseases of the chest to be presented at the Hotel St. Clair, Chicago, September 19-23. It was recommended that greater emphasis be given to cardiac conditions in the next postgraduate course.

The meeting was attended by Dr. James H. Stygall, Regent of the College for the district, and Dr. Italo Volini, the Governor of the College for the state of Illinois. Dr. Andrew L. Banyai, Regent of the College for District No. 10 was one of the guest speakers.

MICHIGAN CHAPTER

On May 4 the members of the Michigan Chapter of the College played host to the members from outside the state at a meeting in Detroit. At 6 00 p m a cocktail party was held which was followed by dinner at the University Club. Fifteen members and four guests were present.

MINNESOTA CHAPTER

The Minnesota Chapter of the College held its annual meeting in St Paul on May 9. Dr John F Briggs, St Paul, was elected President of the chapter for the year 1949-50 and Dr Karl H Pfuete, Cannon Falls, was elected Secretary-Treasurer.

At the request of Dr Hilbert Mark of the State Department of Health, the Chapter decided to establish a speakers bureau on chest diseases. These speakers will be called upon by Dr Mark to address county medical society meetings, luncheon clubs and various lay groups regarding the different phases of tuberculosis control work in the state.

The Chapter voted to collaborate with the University of Minnesota in sponsoring a postgraduate course on diseases of the chest which will be held at the Center for Continuation Study on the University of Minnesota Campus in the fall of the year.

WISCONSIN CHAPTER

Dr Leon H Hirsh addressed the March meeting of the Metropolitan Milwaukee Section of the Wisconsin Chapter on the subject of "Acro-erythrosis." At the April meeting of the Metropolitan Milwaukee Section, Dr Karl E Kassowitz presented a talk on "The Use of Streptomycin in Children."

College News Notes

Dr Edwin R Levine, formerly Director of Chest Service at Michael Reese Hospital, Chicago, and Medical Director of Winfield Sanatorium, Winfield, Illinois, has opened offices for the private practice of medicine at 109 North Wabash Avenue, Chicago. He will specialize in the treatment of diseases of the chest.

Dr Jose Ignacio Baldo, Caracas, Venezuela, Regent of the College, has been appointed a member of the Committee on Tuberculosis of the World Health Organization. The next meeting of the committee will be held in Copenhagen, Denmark on July 26 of this year.

Dr Chester G Crist, Gettysburg, Pennsylvania. Gettysburg College physician for nearly 35 years was awarded the "meritorious service award" for the past year by Gettysburg College. Dr Crist is also jail and county home physician, a post which he has held for the past 15 years, and has served as County Medical Director and Chief of the State Tuberculosis Clinic for the past 25 years.

Dr Robert H Marks has returned to his position as head of the Bureau of Tuberculosis Control of the Territorial Department of Health in Hawaii after a year's absence

The Tuberculosis Committee of the Iowa State Medical Society for 1949 consists of the following members Raymond J Harrington, MD, Sioux City, Chairman, John C Parsons, MD, FCCP, Des Moines, J Carl Painter, MD FCCP, Dubuque, Leon J Galinsky, MD, FCCP, Des Moines, Ralph E Smiley, MD, Mason City, William Spear, MD, FCCP, Oakdale, and Daniel R Webb, MD, Cedar Rapids

A n n o u n c e m e n t

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Minneapolis, Minnesota — October 20-22

Center of Continuation Study, University of Minnesota

3 days — Tuition \$20 00

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New York, N Y. — November 14-19

Hotel New Yorker — 5 days — Tuition \$50.00

Sponsored by the New York State Chapter, American College of Chest Physicians

San Francisco, California — December 5-9

Postgraduate Extension Building, University of California

5 days — Tuition \$50 00

Presented by the California Chapter American College of Chest Physicians, in cooperation with the University of California Medical School and Stanford University School of Medicine

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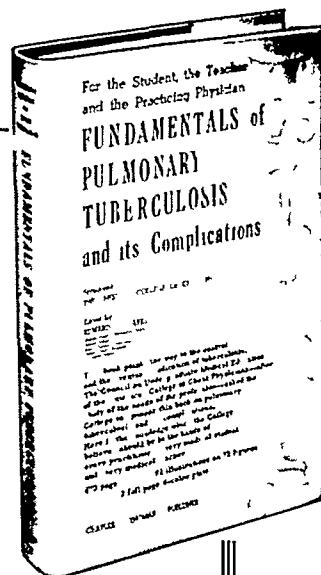
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ROCKY GLEN SANATORIUM CELEBRATES THIRTIETH ANNIVERSARY

On June 16, Rocky Glen Sanatorium, McConnellsville, Ohio, was host to the spring meeting of the Eighth District Medical Society in celebration of the 30th Anniversary of the sanatorium On this occasion, Dr Louis Mark, President-Elect of the College, celebrated his 30th Anniversary as President and Medical Director of Rocky Glen Sanatorium

A scientific program was presented which included a paper by Dr L Chandler Roettig of Columbus on "The Surgical Procedure of Aortic Resection and Anastomosis on Experimental Animals" Dr Mark also presented a talk on "Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis" Other members of the College present at the meeting were Dr C H Benson of Columbus, Dr Frank Lande of McConnellsville, Dr Henry Bachman of Malta and Dr Chester P Swett Lancaster, Councilor for the Eighth District Medical Society

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 Emil Bogen, MD, FCCP
 C Howard Marcy, MD, FCCP
 Andrew L Banyai, MD, FCCP
 Edward William Hayes, MD, FCCP
 Antonio A Adames, MD, FCCP
 Karl H Pfuetze, MD, FCCP
 Horton Corwin Hinshaw, MD
 William H Feldman, DVM
 Charles M Hendricks, MD, FCCP
 Benjamin L Brock, MD, FCCP
 Paul H Holinger, MD, FCCP
 Kenneth C Johnston, MD, FCCP

Ralph C Matson, MD, FCCP*
 William S Conklin, MD, FCCP
 Norman J Wilson, MD
 Richard H Overholt, MD, FCCP
 Herman E Hilleboe, MD, FCCP
 Sumner S Cohen, MD, FCCP
 Gilbert J Thomas, MD
 John N Hayes, MD
 O A Sander, MD
 Major General S U Marietta, MC,
 (Retired), FCCP
 Frank L Jennings, MD
 Henry C Sweany, MD, FCCP
 J Winthrop Peabody, MD, FCCP

*Deceased

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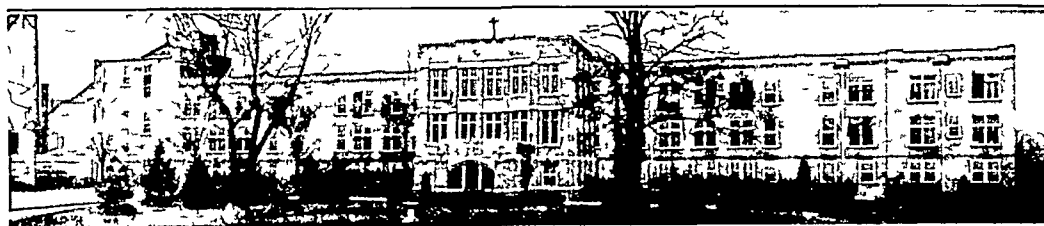
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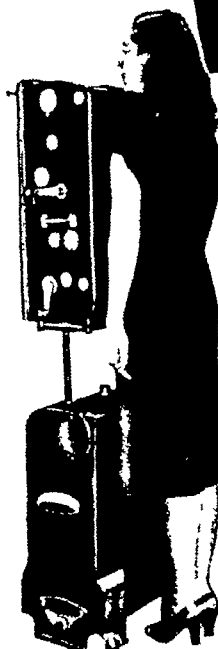
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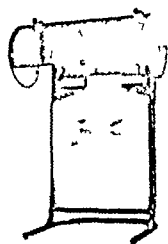
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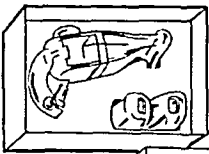
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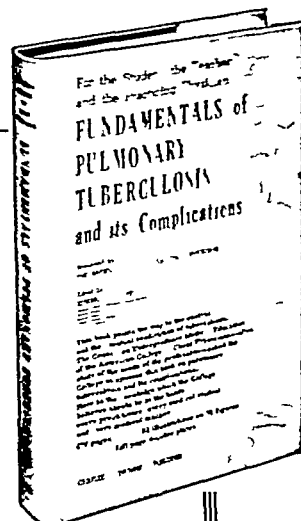
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VOLUME XVI

AUGUST 1949

NUMBER 2

Drainage, Streptomycin and Tuberculosis*

BENJAMIN L BROCK, MD, F C C P

Downey, Illinois

To understand the reason for the usual development and progression of pulmonary tuberculosis in the apex of the lung, or more specifically in the dorsal and cephalic portions of all pulmonary lobes, is to have a better understanding of the pathogenesis of this disease. Having this knowledge, the investigator may evaluate correctly and with satisfaction results obtained in the treatment of the disease.

Macklin has described the "restricted movements of the bronchial tree in the area of the human lung which lies between the root zone and the fixed wall behind and above the root region." It has long been my belief that lack of free drainage from the lungs and bronchial tree in these locations, due to comparative lack of mobility of the lung, is responsible not only for the prevalence of tuberculosis in these locations, but for its progression and chronicity. Detailed explanation of this statement may be found in several published articles by the author since 1938.

The normal cleansing mechanism consists of (1) The cough mechanism (2) The ciliary action, and (3) The peristalsis like action of the bronchial tree during respiration. During inspiration the bronchial tree elongates and the diameters of the lumina of the bronchi become wider. During expiration, the bronchi shorten and their lumina are narrower. This latter mechanism may play a large part in the evacuation of exudates which may accumulate within the bronchial tree and where free drainage is instituted, disease may be prevented, or where disease already exists, it may clear.

*From the Tuberculosis Service, Veterans Administration Hospital, Downey, Illinois. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

Unfavorable conditions affecting adversely the normal mechanism of drainage from the bronchial tree, such as partial blockage by endobronchial tuberculosis, or by peribronchial fibrosis or loss of mobility as in complete consolidation of a lobe, would be conducive to the retention of infectious exudates and the spread of the disease. This is purely mechanical and has nothing to do with lack of immunity of the individual.

The secret to the favorable results which may follow collapse therapy is the institution of free and adequate drainage of infectious exudates from the lungs and bronchial tree. This statement has been made by the author in a number of published articles since 1940.

The mechanics of the collapse in artificial pneumothorax is different, however, to that of artificial pneumoperitoneum. In my opinion, artificial pneumothorax is contraindicated in the presence of endobronchial disease. Bronchoscopic examination should be made where pneumothorax is being considered. By so doing, atelectasis and inexpandable lung, as a result of it, may be prevented. Where tension cavity is present, artificial pneumothorax usually makes matters worse. Compression over the cavity narrows the already partially blocked bronchus leading to the cavity with the result that the blockage becomes more complete, the cavity becomes larger and under greater tension. Air can still enter on inspiration, but on expiration, the air can not escape. When such cavities close following re-expansion of the lung, the cause is believed to be due to the re-establishment of adequate drainage through an alteration of the check valve mechanism. This is accomplished through a widening of the lumen of the bronchus leading to the cavity.

Pneumoperitoneum with or without phrenemphraxis has a remarkable effect on the closure of tension cavities. Not only is the check valve mechanism altered following this procedure, but drainage of infectious exudates from the lungs and bronchial tree is facilitated. This free drainage of exudates also allows for healing of the endobronchial lesion, since retention of infectious exudates at the site of its development is considered to be the chief factor in its pathogenesis.

The optimum level of the diaphragm in pneumoperitoneum patients is that level which permits of absolute ease of expectoration. After studying clinically large numbers of pneumoperitoneum patients in recent years, it has become increasingly clear that the ease of expectoration or the free drainage which occurs following the induction of therapy is the secret to the clearing of the pathological process. One cannot but be impressed also by the fact that rarely does bronchogenic spread occur when free

and adequate drainage exists. In these studies, it has frequently been observed that drainage may be made so free in acute bilateral advanced disease with tension cavity formation in the negro, that complete clearing of the disease occurs. Such disease has in the past been considered the type which eventuates in fatality. Certainly no other form of collapse therapy at our disposal has produced such remarkable results. Such results should modify our beliefs relative to the pathogenesis of pulmonary tuberculosis.

A large factor affecting adversely the drainage mechanism in the negro is the loss of mobility of the lung due to the frequent occurrence of consolidation.

Artificial pneumothorax should not be given in acute pneumonic tuberculosis nor in cases associated with endobronchial disease. The indications for artificial pneumothorax today are limited. In my opinion pneumoperitoneum not only has wider indications, but its use is accompanied by fewer serious complications.

Having discussed at some length the normal mechanism of drainage from the lungs and bronchial tree and how it may be assisted by collapse therapy, it will be my endeavor to show how drainage combined with streptomycin influences the course of tuberculous processes not only in the lungs, but in various locations of the body.

Streptomycin and Drainage in Pulmonary Tuberculosis

It has been observed on numerous occasions that young individuals with fresh pneumonic tuberculosis respond unusually well to streptomycin therapy. Some of these patients in fact go on to complete clearing of the pathological process. On the other hand, individuals who have developed fibrotic changes with or without cavity formation and who also have an exudative component do not respond as well to streptomycin therapy. There is evidence to show that streptomycin through its suppressant action on the tubercle bacillus retards the formation of exudates. In the individual with fresh pneumonic tuberculosis without fibrotic changes, free drainage usually follows streptomycin therapy and continues unhampered through an unchanged anatomical bronchial tree. Most of these patients who have had difficult expectoration previous to therapy begin to expectorate freely and with ease after therapy has been started.

If early and adequate drainage is not brought about in these cases, however, permanent productive and fibrotic changes take place in the lung. In such cases the drainage mechanism becomes permanently altered. This fact not only accounts for less favorable results following streptomycin therapy in these cases, but

it is also believed to account for the more frequent recurrences of active disease

In chronic pulmonary tuberculosis, it is not unusual to see a clearing of a fresh pathologic process in one area of the lung and a spreading of the process in another. This can be explained on the basis of adequate drainage on the one hand and inadequate drainage on the other.

It has been generally accepted that streptomycin therapy in conjunction with collapse therapy in this type of case is the treatment of choice. The mechanism of drainage brought about by collapse therapy has been described above. In some advanced pneumonic cases in the negro, it may be impossible to initiate adequate drainage following streptomycin therapy because of the solidity of the lung. The outcome in such cases is regularly unfavorable.

Streptomycin and Drainage by Cavernostomy

Giant cavities will occasionally close following the introduction of artificial pneumoperitoneum. Where this does not occur, however, following a trial period of six months open cavernostomy combined with streptomycin therapy should be tried. Surgeons in the past have not accepted cavernostomy as a method of choice in the treatment of giant tension cavities or residual cavities following thoracoplasty because of technical difficulties and dangers which accompany the operation. The chief reason why cavernostomy has not been looked upon with favor, however, is perhaps because adequate drainage was not effected over sufficient time to render the drainage material negative for tubercle bacilli. The Eloesser technique of open drainage of tension cavities has recently been used with considerable success and no doubt because the above requisites have been met. Murphy et al, have recently reported excellent results in the use of the Eloesser technique of open cavernostomy combined with streptomycin in 11 patients with residual cavities following thoracoplasty. The sputum was converted in 10 of the patients and six of the sinuses closed without surgical aid. One of the patients died.

Four open cavernostomies have been performed in this hospital recently with striking clinical results. One of them deserves special mention as follows. T.K., age 22, was admitted to the hospital on May 3, 1948, with a diagnosis of far advanced pulmonary tuberculosis and laryngeal tuberculosis. There was a giant tension cavity in the right apex, and a recent bronchogenic spread to the left lung. The symptomatology and the type of spread were typical of those seen so frequently in association with endobronchial disease and tension cavity. Streptomycin therapy tempo-

rarily relieved to some extent the symptomatology, and there was a clearing of the process in the left lung. Six weeks after the beginning of streptomycin therapy, a spread on the left side to its original intensity had occurred. Closed cavity drainage with continuous suction instituted on July 15, 1948, was ineffective and at the time of removal of the tube on August 23, 1948, x-ray films revealed a spread to the right base. Another course of streptomycin was given, and during treatment an x-ray film taken on September 13, 1948, revealed an extension of the pathological process to have taken place, under the cavity on the right side. At this time a high degree of resistance of the tubercle bacilli to streptomycin had developed. Since admission to the hospital, the patient had been clinically active with elevation of temperature, irritable cough with difficult expectoration, and had shown continuous spread of the disease. His appetite had been poor and he had lost weight. There had been improvement, however, of his laryngeal tuberculosis. An Eloesser type of cavernostomy was performed following the second course of streptomycin therapy, and since that time drainage has been free. At first it was purulent and copious. At present it has diminished considerably in amount and is thinner in consistency. The patient no longer has difficult expectoration and is clinically non-active. He has a good appetite and is gaining in weight. The x-ray films recently have shown continuous clearings and the cavity has diminished greatly in size. This demonstrates dramatically the role that free drainage plays in active pulmonary tuberculosis—even where a high resistance of the organisms to streptomycin has developed.

Streptomycin and Surgical Drainage of Tuberculous Sinuses

One of the most impressive results in the treatment of tuberculosis in man by streptomycin has been obtained following its use in draining tuberculous sinuses. In the original article published on this subject by the author, it was recognized that closure of the sinuses was more prompt when free drainage was present. It was demonstrated that when small abscesses exist under the skin and the sinuses are not draining adequately, the areas should be incised and the pus evacuated. It has also been shown that where necrotic bone or cartilage is present, as for example in a rib or sternum, this necrotic material should be removed. When this is done, streptomycin accelerates healing.

When a large cold abscess exists in conjunction with tuberculosis of the vertebrae, there is little tendency for the pus to disappear under streptomycin therapy unless it is evacuated by open drainage. When, however, the large surgically made sinuses are allowed to drain while streptomycin therapy is being carried

out, they fill in quickly and close. Healing in 95 per cent of sinus cases treated with streptomycin may be obtained where free surgical drainage exists, otherwise the percentage of healing is not so great.

Streptomycin and Excision Surgery for Fistulae

Fistulae do not respond nearly so well to streptomycin as do sinuses when treated without surgical intervention. However, where the fistula is excised the lesion completely heals and remains so. Of the original series of 15 fistulae excised at Veterans Hospital, Oteen, North Carolina, and reported by Murphy, 100 per cent healed. Since that time this author treated 19 cases of rectal fistulae with streptomycin and resection therapy. Seventeen of these healed and two improved.

Streptomycin in the Treatment of Tuberculous Lesions Located on Surface Areas

It has been frequently observed that tuberculous lesions occurring on the tongue or in canalicular organs such as the larynx, the bronchi, and the intestines heal readily under streptomycin therapy. On such surface areas, free drainage may occur from the lesions following the suppressant action of streptomycin on the offending organism with the result that a high percentage of healing takes place.

On the other hand, lesions in other organs such as the brain and kidneys do not respond as well to therapy, partially at least because of the absence of these free drainage facilities. Although the immediate results obtained in the use of streptomycin in tuberculous meningitis have been outstanding, the eventual outcome in these cases is relatively poor. It is believed that the original caseous foci within the brain substance may emit showers of tubercle bacilli which in turn would be responsible for the recurrence of active tuberculous meningitis. According to Baggenstoss, Feldman and Hinshaw, streptomycin does not penetrate the substance of the brain in appreciable amounts, and for this reason would have no influence on the bacilli within the caseous foci. From a theoretical standpoint, one might assume under these conditions that the bacilli within the caseous foci in the brain would always remain sensitive to streptomycin provided these foci were in fact original foci and had never made contact with streptomycin. It would also be logical under these conditions to continue streptomycin therapy over a much longer period of time than is the custom at present in this country. Such a course of therapy might prevent recurrences of meningitis in that the strep-

tomyacin would have immediate effect upon bacilli which might be emitted from the original foci

Flory et al, and Auerbach and Stemmerman have observed healing tubercles in the pons and the former infer that streptomycin must have been responsible for the healing, which is contrary to the belief of Baggenstoss, Feldman and Hinshaw. However, the small amount of healing that has been observed in the substance of the brain may be due in part to the lack of drainage from the brain

CONCLUSION

In conclusion, it is of interest to speculate on the possible correlation between the degree of drainage from a tuberculous focus located in any part of the body, and the development of resistance of tubercle bacilli to streptomycin

In general it has been shown that when clearing of the lesion is taking place in a satisfactory manner, resistance of the organisms to streptomycin does not develop. Conversely where streptomycin does not affect an early favorable result, an increasing resistance of the organisms is the rule. A lack of adequate drainage may play a definite role in the development of resistance

CONCLUSION

En conclusión, es interesante especular sobre la posible correlación entre el grado de canalización de un foco tuberculoso localizado en cualquier parte del cuerpo y el desarrollo de resistencia del bacilo tuberculoso frente a la estreptomicina

En general, se ha demostrado que cuando la limpieza de la lesión ocurre de manera satisfactoria, la resistencia del organismo a la estreptomicina no se desarrolla

Inversamente cuando la estreptomicina no afecta una lesión tempranamente, un aumento de la resistencia de los gérmenes es la regla

Una falta de adecuado drenaje puede desempeñar un papel definido en el desarrollo de resistencia a la estreptomicina

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The Physiological Significance of Bronchiectasis*

DUANE CARR, MD, F C C P, EDWARD F SKINNER, MD,
WM E DENMAN, MD and CHAS R KESSLER, MD **

Memphis, Tennessee

Bronchiectasis is a disease characterized by pathological enlargement of one or more bronchi or bronchioles. The dilatation per se, however, is not the most important pathological factor. The dilatation is only the demonstrable effect of a pathological process which damages the tissues of the lungs and bronchi sufficiently to interfere with their function.

Pathology

Examination of bronchiectatic bronchi reveals the loss of normal columnar ciliated epithelium. This is replaced in some instances by purely cicatricial tissue, and in others by a stratified squamous cell epithelium. The basement membrane of the mucosa is likewise destroyed or damaged, and elastic tissue fibers disappear. The submucosa, normally a loose fatty connective tissue, becomes densely fibrotic and rigid. In the immediately adjoining lung parenchyma there appears to be laid down additional fibrosis which adds to the thickness and rigidity of the bronchial wall.

Associated with bronchiectasis one finds varying degrees of pulmonary atelectasis, pneumonitis and sclerosis. In advanced cases the affected lobe or lobule may be small, firm and contracted. There is no absolute knowledge as to whether the bronchiectasis is advanced because it exists in such a lobe, or whether the advanced bronchiectasis causes the lobe to assume these characteristics. If impairment of function is considered, it appears probable that each factor plays upon the other, producing a progressive and vicious cycle of events.

Physiology

To visualize the importance of the cleansing mechanism of the lungs and bronchi, observe a wire screen through which an exhaust fan has been blowing for a few days or weeks. Or consider a filter removed from an air conditioning unit after a season's use. It is the same air passing through each that must be inhaled, and it is apparent that without an effective means of self cleans-

*Presented at the 6th Annual Meeting of the Southern Chapter, American College of Chest Physicians, October 25, 1948, Miami, Florida.

**University of Tennessee College of Medicine, Department of Medicine and Surgery.

ing, the bronchi would become completely clogged within the first few months of life

The major air passages from the trachea to the bronchioles are normally supplied with a columnar ciliated epithelium, and mucous and serous glands. Foreign particulate matter is enveloped in mucus and steadily swept towards the larynx by the cilia. A portion of the dust, dirt and pathogenic organisms is disposed of in this manner.

Peristaltic waves have been observed in the bronchi and are thought by some to play a part in the evacuation of secretions containing foreign or noxious matter.

Phagocytic leukocytes have been shown to ingest particles which reach the alveoli, and, with an amoeboid type of movement, to pass through the alveolar walls to enter the lymphatic streams. Through one system of lymphatic channels the undesired particles are carried to and deposited in the lymphatic glands located at the various bifurcations of the bronchial tree. Through the other, they are carried towards the periphery of the lung to be deposited beneath the pleura.

Perhaps the most important of all the protective mechanisms is the cough reflex, stimulated by the presence of a foreign substance in contact with the sensitive bronchial mucous membrane, or by the exclusion of air from a bronchus, as by the insertion of a bougie or the presence of a foreign body, a tumor or plug of mucus. The cough itself is picturesquely described by Chevalier Jackson as consisting of "the tussive squeeze and the *becchic* blast," which implies the necessity of air passing beyond the material to be evacuated (into alveolar air spaces) in order to provide the motivating force for its movement towards the mouth.

Consideration of the anatomical pathology found in bronchiectasis indicates at once the functional impairment to be overcome. The ciliated epithelium is destroyed and is not replaced. The rigidity of the walls of bronchiectatic bronchi precludes any possibility of bronchial peristalsis taking place. The atelectasis, pneumonitis or sclerosis of the surrounding lung parenchyma prevents the admission of air which would play an important role in the expulsion of mucus, pus or foreign material from the damaged bronchi through the medium of coughing. These bronchi, then, are inert receptacles which will retain and which will not expell infection and its byproducts without help. They are truly the "cesspools of the lungs."

It is to be expected that bronchiectasis should be a progressive disease. In an involved lobe the retention of infection produces further destruction of and damage to the tissues of the bronchi and lung parenchyma. With increasing fibrosis and rigidity of

the bronchial walls and lung parenchyma, drainage by means of coughing is still further impaired. Unless measures are taken to prevent it, the constant presence of infected secretions overflowing into adjoining bronchi, or being coughed into distant bronchi, constitutes a menace to previously healthy and normal bronchi.

Etiology

Several theories have been put forth regarding the mechanism which produces ectasia of the bronchi. Barring congenital anomalies, all of them contain two factors in common with one another: infection plus interference with the normal mechanism of bronchial cleansing.

The "mechanical pressure of stagnant secretions" of Laennec implies bronchial obstruction, whether it be due to a foreign body, neoplasm, luetic or tuberculous stricture, or sticky mucoid secretions. Broncholiths, collections of detritus and the closure of bronchi due to pressure are also agents which contribute to the development of bronchiectasis in the presence of infection.

The theory of "nutritional changes in the bronchial wall" proposed by Andral suggests a malfunction of the cilia and impairment of resistance of the tissues to infection. More recent observations on the value of Vitamin A in the healing of bronchial ulcers lends some support to the idea that susceptible bronchi are unhealthy or lack normal metabolism.

Stokes writes of the paralysis of the circular muscle fibers of the bronchi with subsequent loss of ciliary action and atrophy of the musculature as an etiological factor.

Pulmonary fibrosis or "cirrhosis pulmonum" was a principal factor in the production of bronchiectasis according to Corrigan, although it was his belief that the enlargement of the bronchi occurred as a result of direct pulsion or traction upon the bronchi. It is equally logical to assume that the fibrotic lung interferes with the cough mechanism sufficiently to interfere with bronchial drainage. Indeed, we have repeatedly seen bronchiectasis develop in the region of a thickened and immobile pleura following chronic empyema.

We have been still further impressed with the importance of impairment of bronchial cleansing in the production of bronchiectasis in a group of over two hundred patients (to be reported in detail in another communication) who had suffered exposures to mustard gas in the last war or exposures of sufficient severity to cause chemical burns of the bronchial mucous membrane with destruction of the ciliated epithelium. We have had the opportunity to make bronchograms on all of these patients, some of them repeatedly over the past four years, and to bronchoscope

many of them, taking biopsies of the bronchial lining. All of the patients with proved exposure have developed a severe bronchitis characterized in the bronchograms by a roughening of the bronchial contours. A large majority of them are developing bronchiectasis. Several have asthmatic symptoms with the production of a marked pulmonary emphysema.

It is significant to note that those patients with impaired bronchial drainage as indicated by loss of ciliated epithelium from the biopsy specimens and roughening of the bronchial walls on bronchograms suffer as severe symptoms and disability as do those who show evidence of true cylindrical and saccular dilatations of the bronchi. It forms the basis for our contention that the dilatation per se is not so important a factor as the functional impairment in bronchiectasis.

Diagnosis

It is not within the scope of this paper to discuss in detail the diagnosis of bronchiectasis. The characteristic history, physical findings and laboratory data are well described in many text books.

We would like to emphasize, however, the importance of good bronchograms in proving the diagnosis. Since bronchiectasis may exist in isolated segments, a good distribution of oil must be obtained. It should be so introduced and the patient sufficiently anesthetized that it is possible to fill the bronchial tree without producing a cough which clouds the picture by blowing oil into the alveoli. The x-ray films must be sufficiently penetrated to show the iodized oil through the heart shadow and behind the diaphragm. The patient should be positioned so it is possible to identify each affected segment of each lobe.

Having tried all known methods of making bronchograms, the authors have found the "dribble method" as effective as any of the more complicated procedures, at the same time causing less discomfort to the patient and requiring a minimum of time. The procedure consists of simple seating the patient on a stool in front of a fluoroscope and dribbling two eyedropperfulls of one half per cent pontocaine through one nostril while the tongue is held extended and the patient breathes through his mouth. The solution is directed by tilting the patient laterally, first to the right and then to the left. Immediately following this, the warmed iodized oil is slowly instilled in the same fashion over the course previously anesthetized by the pontocaine. When fluoroscopy shows that the desired bronchi have been well filled, appropriate x-ray films are immediately made.

In our experience, if bronchiectasis is present it can usually be demonstrated at one sitting with the use of 20 cc. of iodized oil.

This is adequate to fill the lower lobe, middle lobe and lower branches of the upper lobe on the right, together with the entire lower lobe, lingula and a few other branches of the upper lobe on the left. At this original examination the right lung is filled first so that a right lateral film will demonstrate the lobar and segmental distribution of the oil without interference from shadows in the contralateral lung. It is much easier to identify the bronchi on the left from the ensuing postero-anterior film, at least adequately for the original diagnosis. When resection is contemplated, the bronchograms are readily repeated directing the oil into those branches not previously filled and making the appropriate films to demonstrate the segmental distribution of the bronchiectasis present.

We are beginning to believe that when some type of resection is anticipated from the start, it is perhaps best to fill one lung completely and obtain postero-anterior and straight lateral x-ray films, followed in a few days by this same procedure on the contralateral side. This gives us our best conception of the segmental distribution of pulmonary disease. Utilizing a procedure as simple as the "dribble method," requiring less than 15 minutes, there is no objection to this very effective two stage procedure.

Treatment

Medical treatment of bronchiectasis consists of a routine of mechanical aid to the cleansing of the bronchi, combined with appropriate chemotherapy, and general support. Postural drainage at frequent intervals is essential, supplemented by expectorants such as ammonium chloride, gr LX, daily and a high fluid intake to keep the bronchi moist. Since the damaged bronchi are incapable of rejecting the coal tar by-products of smoke, the patient cannot indulge in smoking. Repeated bronchoscopic aspirations of secretions are useful in some advanced cases. The choice of sulfa drugs, penicillin or streptomycin depends upon the flora demonstrated in sputum cultures, but all are reserved for those periods during which the patient most greatly needs them. General resistance is maintained by assuring the patient a high red blood cell count and hemoglobin, high protein and adequate vitamin intake.

Surgical therapy consists of removing involved lobes or segments of lobes after complete mapping of the bronchial tree with bronchograms indicates that the disease process is limited to areas of not too great extent to be totally excised. The advent of segmental resection has enlarged the group of patients who may be permanently relieved of their disease by surgical means.

All forms of collapse therapy are to be condemned as dangerous.

and ineffective, except the occasional use of a temporary phrenic nerve interruption to check hemoptysis

SUMMARY

The enlargement of the bronchi is not the significant aspect of the disease called bronchiectasis. Of greater importance is the loss of the cleansing mechanism of the bronchi, leading to the retention of infection, mucus and foreign matter. Retention causes progression of the disease, toxic absorption, recurring pneumonitis and many other complications.

Treatment is directed especially towards *providing drainage constantly*, supplemented by chemotherapy and all supportive measures which will increase the resistance of the patient. Where resection of all involved lobes or segments of lung is feasible, it offers permanent cure of the disease.

RESUMEN

En ensanchamiento de los bronquios no es el aspecto significativo de la enfermedad llamada bronquiectasia. De mayor importancia es la pérdida del mecanismo de limpieza de los bronquios lo que conduce a la retención de la infección, del moco y de los cuerpos extraños. La retención produce el progreso de la enfermedad, la absorción tóxica, la neumonitis recidivante y muchas otras complicaciones.

El tratamiento se dirige especialmente hacia el fin de proporcionar canalización constantemente complementada con la quimioterapia y por todas las medidas auxiliares que aumenten la resistencia del enfermo. Cuando la resección de todos los lóbulos o segmentos del pulmón enfermos es practicable, esto significa una cura permanente de la enfermedad.

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D I S C U S S I O N

RALPH ADAMS, M.D., F.C.C.P.
Woodbury, Tennessee

The point made about fibrosis in the areas surrounding the dilated bronchi is a critically important one. I am afraid that in

the last year, more patients have been harmed by segmental resection than were helped by it Up until the last year, I think the reverse was true and the reason is that too many surgeons have tried to become prima donnas and see how little bronchiectasis they can remove instead of how much It is true that the segment can sometimes be taken as the pathological unit of the lung as it is the functional unit but from a surgical standpoint you must remember that the division as distinguished from the segment is usually the smallest acceptable resective unit

The second point about cough sensitivity, is absolutely true There is a simple test which you can make yourself if you will through your bronchoscope and see the exudate welling back and forth in the primary bronchus, patient not coughing, although scarcely anesthetized If you put India ink into a patient's normal lower bronchus, in five minutes you will see definite progression of that ink upward In the chronically diseased bronchus, you will not, we have carried it for as long as 15 minutes

The third point which Dr Carr indicated but did not stress, from a physiological point of view, is an observation from point of time It can be stated axiomatically as it has been before, if a patient has bronchiectasis before he is 10, he will be dead before he is 40 for the reason that he indicated, the persistence of fibrotic tissue that might well have been removed in the beginning

DAVID H WATERMAN, M.D, F C C P
Knoxville, Tennessee

I would like to mention a personal debt to Dr Carr that I have always felt In 1941 he showed me his method of introducing oil into the bronchial tree and emphasized the importance of stereos I think all of us have come to the point where we use very few stereo x-rays at the present time routinely but certainly with a well built bronchial tree, a stereo is a beautiful sight to behold and the individual branches that are involved stand out so clearly that until you have seen one, you can't appreciate the value of a good bronchogram

I would also like to mention that the point he made of filling all segments of the bronchial tree cannot be overemphasized because from a surgical standpoint, we want to know exactly which bronchi are involved, either to a greater or lesser extent, and which ones are negative The negative information is just as important as the positive

ALFRED GOLDMAN, M D , F C C P
St Louis, Missouri

I would like to ask whether bronchiectasis is a progressive disease Has Dr Carr ever actually watched dilatations in new portions of the lung that weren't there when he first saw the case I am asking about chronic bronchiectasis

JOHN S HARTER, M D , F C C P
Louisvill, Kentucky

I would like to ask Dr Carr what the significance is and the cause of nodulation that sometimes is seen in bronchiectasis in cases that are rather progressive, they are going downhill, losing weight, etc

Closing Remarks

Duane Carr, M D , F C C P , Memphis, Tennessee We have tried all known methods of making bronchograms, even to the injection of oil directly by needle into the trachea and which we subsequently abhorred We passed catheters, both bronchial catheters and intratracheal tubes, and in the adult or in the cooperative patient, we have found the most satisfactory method to be the simple dribble method The medicine dropper is put just inside the nares, the tongue is held out and the patient is requested to breathe through the mouth and the tongue is held to prevent swallowing About two droppers full of one-half per cent pontocaine with 10 drops of adrenalin mixture is instilled into the nostril with the patient tilted to one side, and then the same procedure with the patient tilted to the contralateral side Then the warmed oil in the syringe with a rubber tip is used and the tip of the catheter is passed over the first hump of the nares The oil is allowed to run back the pharynx with deep quiet breathing Oil doesn't run by gravity in the upper lobes but it is drawn in these lobes by the respiratory act, and you can fill them perfectly well by simply tilting the patient and the lobe into which the oil is guided is controlled entirely by position of the patient

The deep quiet breath means that if the patient is breathing quietly without making any rasping noise, the larynx is relaxed and open The oil runs in freely The oil is instilled at the rate of about 1 cc for every two breaths Then of course we have fluoroscoped the patient to see when we have an adequate filling or have filled the portion of the lung we most particularly desire

You will never get oil pneumonia if you empty the oil out immediately after getting the bronchogram

We make no attempt to fill the entire bronchial tree at one sitting. One of us had that done to him and the dyspnoeic effect was truly distressing, and consequently in our ordinary diagnostic screening of bronchograms, we fill both lowers, the right middle, the lower segment and both uppers at the first sitting. Now if we contemplate surgery from the start, we will fill one lung completely and make PA and lateral films and at a different sitting entirely fill the other lung and make PA and lateral films. The total procedure from anesthetization to the taking of the films takes not over 10 to 15 minutes. There is no valid objection to dividing it in that fashion.

Dr. Waterman is quite correct that when we make stereoscopic films, it is easy to identify all of your segments individually and in at least one instance we showed a persistent block of a peripheral bronchus by stereoscopic film that we never would have spotted on ordinary examination. I am in perfect agreement with what Dr. Adams said in not going overboard for segmental resections when the segment showed dilatation and there was damage in the adjacent segments of the bronchi. In regard to Dr. Goldman's question we have seen repeatedly, particularly in mustard gas cases, progression of bronchiectasis from one segment to another. In one case there had been sufficient bronchiectasis in spite of measures directed at treating it that death ensued.

Adenoma and Cylindroma of the Bronchus*

WILLARD VAN HAZEL, MD, FCCP,
PAUL H HOLINGER, MD, FCCP and
ROBERT J JENSIK, MD **

Chicago, Illinois

The subject of bronchial adenoma and cylindroma remains a highly controversial one. Despite differences of opinion as to origin, nomenclature, pathology, malignancy or benignancy, and treatment much has been learned about these unusual tumors, mainly through the cooperative efforts of endoscopists, surgeons, and pathologists. The various series of cases reported in the literature have done much to make clinicians and pathologists aware of the specificity of these entities and to narrow the points of disagreement among those who work in the field of thoracic disease.

This paper consists of an analysis of 20 cases of adenoma and two of cylindroma that have been seen during the past 12 years. Table I summarizes the age, sex, symptoms, duration, roentgen findings, bronchoscopic findings, diagnosis, treatment and end results of these patients. Several are discussed in greater detail to emphasize important features of the symptomatology, bronchoscopic aspects, histopathology or treatment.

Representative Cases

Case 5 G W This patient, a 25 year old white male, developed pleurisy in 1933 for which aspiration of the chest and adhesive strapping were done. Studies for tuberculosis were negative and in the next six years frequent colds and fever were present during the winter months. In 1939 he had his first hemoptysis with repeated attacks occurring in the next three months. On physical examination the percussion note, fremitus and breath sounds were reduced over the entire left chest. Roentgen and lipiodol studies revealed a density of the entire left chest considered to be both atelectatic and inflammatory in nature. Bronchoscopic examination revealed a polypoid tumor arising from the left main bronchus proximal to the left upper lobe orifice. Biopsies were reported as diffuse small round cell carcinoma. A left pneumonectomy was done on August 1, 1939. The patient expired on the eighth postoperative day following the sudden development of tension pneumothorax.

Pathology A study of the resected lung showed the tumor to be 15 mm in diameter, it was attached to the wall of the main bronchus over an

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area measuring 5-10 mm in diameter. The distal bronchi were filled with varying amounts of foul mucopus and blood. Microscopically the tumor was composed of "a disorderly, diffuse proliferation of small to medium sized faintly granular cells with deeply staining irregular nuclei. They are occasionally found in cord-like or alveolar arrangements." There were two spicules of bone also present, and at the base of the tumor there was invasion of the bronchial wall. The hilar nodes were negative for tumor (Figs 1 and 2). The diagnosis was "Bronchogenic Carcinoma." The autopsy failed to reveal any evidence of distant metastases. The cause of death was acute empyema secondary to left bronchial fistula and acute fibrinous pericarditis.

Review of the biopsy and surgical specimen slides have resulted in changing this to a final diagnosis of adenoma of the bronchus. The uniformity of the cells with tendency to glandular pattern separated by their connective tissue stroma can be seen in the photomicrograph. In figure 2 invasion into the wall of the bronchus can be seen. Of significance is the proximity of tumor tissue to a large caliber vessel. Bone spicules are also seen but they are representative of adult and not neoplastic bone. In view of our present concepts of bronchial adenoma, this case can justly be classified as a typical adenoma.

Case 13 EO This patient is a 34 year old white female who had complained of bronchitis with cough and sputum for six years. She had attacks of pleurisy and two years before entering the hospital thoracotomy was done for empyema. Subsequently she had repeated attacks of cough and sputum with episodes of fever and hemoptysis. Physical findings revealed diminution of the percussion note and breath sounds over the entire left lung, roentgen films showed a marked pleural density

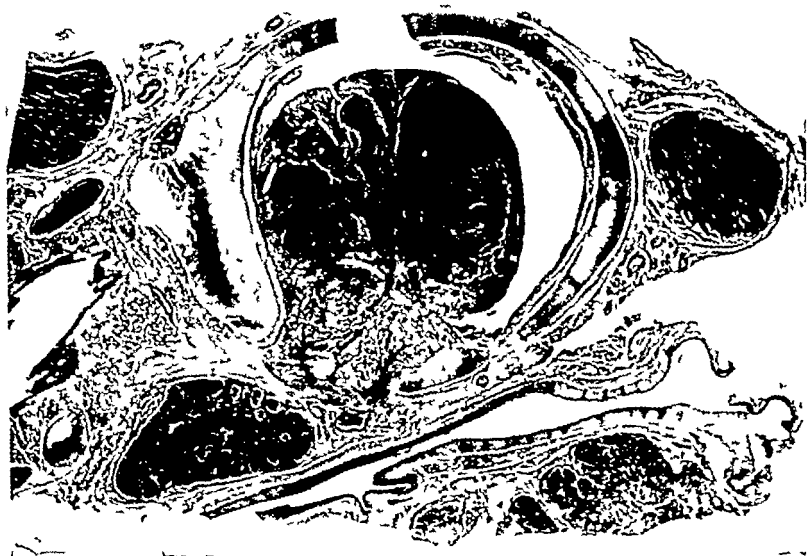


FIGURE 1 Case 5 (5X) Cross section of tumor in the left main bronchus. Note broad base of tumor and relation to cartilage, large vessel and adjacent lymph nodes. No tumor present in the bronchial nodes.

TABLE I

Case	Age	Sex	Symptoms	Duration	Roentgen Findings	Bronchoscopy Findings	Histopathology	Treatment	Result	Final Diagnosis	
1	M S	50	F	Pneumonia 10 mos ago, cough, sputum, hemoptysis	10 mos	Density, left lower lobe	Obstruction, left lower lobe bronchus	Adenoma	Lobectomy, left lower lobe	Death - 3rd day, cardiac failure	Adenoma
2	H V K	36	F	Recurrent pneumonia with cough, sputum, hemoptysis	5 yrs	Atelectasis, right lower lobe	Polypoid tumor right bronchus below middle lobe orifice	Small cell bronchogenic carcinoma	Right pneumonectomy	Well 7 yrs	Adenoma
3	G L	53	M	Cough, episodes of fever and hemoptysis	5 yrs	Triangular density—left base posterior chest	Tumor obstructing lower lobe bronchus	Adenoma	Left lower lobectomy	Well 1½ yrs	Adenoma
4	C B	36	F	Recurrent pneumonia, cough, fever, hemoptysis	16 yrs	Atelectasis, left lower lobe	Tumor obstructing left lower lobe bronchus	Carcinoma (1927) Adenoma (1936) Mixed tumor of bronchus (1941)	Pneumonec-tomy (1941)	Well 7 yrs	Adenoma
5	G W	25	M	Cough, sputum, hemoptysis	6 mos	Density, left upper chest, partial atelectasis, left lower lobe	Tumor, left main bronchus, level of upper lobe orifice	Small round cell carcinoma (1938)	Pneumonec-tomy (1939)	Death 6 POD	Adenoma
6	S J	63	F	Cough, chills, sweats	Many years	Atelectasis middle lobe	Tumor within middle lobe orifice	Carcinoma Adenoma	Pneumonec-tomy	Well 2 yrs	Adenoma
7	C J	31	M	Cough, episodes of streaked sputum	Several years	Atelectasis, left lower lobe	Obstruction, lower lobe bronchus	Adenoma	Left lower lobectomy	Well 2½ yrs	Adenoma
8	C G	49	F	Pneumonia Hemoptysis Cough	3 yrs 3 yrs 3 yrs	Right upper lobe atelectasis	Obstruction, right upper lobe bronchus	Adenoma	Endoscopic Removal	Well 4½ yrs	Adenoma
9	L S	40	M	Cough, episodes of fever	10 yrs	Atelectasis right upper lobe	Tumor mass obstructing right bronchus	Granulation tissue	Pneumonec-tomy	Well 2 yrs	Adenoma
10	E S	26	F	Wheeze, pneumonia, hemoptysis	3 yrs	Atelectasis, right upper lobe	Tumor obstructing right main, originally from right upper lobe	Adenoma	Pneumonec-tomy	Well 4 yrs	Adenoma

11	CH	50	F	Cough wheeze	2-3 yrs	Atelectasis left lung	Obstruction left main bronchus 1½ cm beyond coryna	Adenoma	Pneumonec-tomy	Well 4 yrs	Cylindroma
12	LM	53	F	Cough hemoptysis	1½ yrs	Atelectasis right lung	Tumor mass at coryna obstructing right main bronchus	Carcinoma Adenoma	Repeated bronchoscopy	Death 5½ yrs Hemorrhage and asphyxia	Cylindroma
13	EO	34	F	Cough sputum pleurisy empyema and hemoptysis	6 yrs	Density atelectasis, left lung	Obstruction left main bronchus 1½ cm beyond the coryna	Adenoma	Pneumonec-tomy attempted, thorocoplasty and cauterization	Well 5 yrs	Adenoma
14	RH	49	F	Cough wheezing	1 yr	Atelectasis right lower lung field	Pedunculated mass from right middle and lower lobe spur	Adenoma	Bronchoscopic removal 2x	Well 5 yrs	Adenoma
15	EB	35	F	Cough hemoptysis	1 yr	Atelectasis left lower lobe	Obstruction lower lobe bronchus	Adenoma	Bronchoscopic removal	Well 2½ yrs	Adenoma
16	RH	30	F	Cough sputum hemoptysis	6 mos	Atelectasis right lower lobe	Obstruction right lower lobe bronchus	Adenoma	Bronchoscopic removal 2x	Well 6 yrs	Adenoma
17	LL	32	M	Cough sputum	3 mos	Atelectasis right upper lobe	Polypoid mass from right upper lobe	Adenoma	Repeated bronchoscopic removal 7x	Well 4½ yrs	Adenoma
18	JK	48	M	Cough sputum hemoptysis	5 yrs	Atelectasis right lower lobe	Obstruction right lower lobe bronchus	Adenoma	Refused treatment	Living	Adenoma
19	RM	34	F	Cough sputum streaking	2 yrs	Atelectasis left upper lobe	Obstruction left upper lobe orifice	Adenoma	Repeated bronchoscopy	Not seen 3 yrs	Adenoma
20	JS	50	F	Cough hemoptysis	9 yrs	Atelectasis right lower lobe	Obstruction right lower lobe	Adenoma	Bronchoscopy twice	Not seen 3 yrs	Adenoma
21	ML	34	F	Cough sputum hemoptysis	7 yrs	Density lower left chest	Obstruction left lower lobe	Adenoma	Repeated bronchoscopy	Improved	Adenoma
22	TM	35	F	Cough hemoptysis	4 yrs	Density entire left lung	Left main bronchus	Adenoma	Repeated bronchoscopy	Improved	Adenoma

with little aerated lung on the left side. Bronchoscopy demonstrated a polypoid tumor in the left main bronchus which produced complete obstruction 15 centimeters distal to the coryna. Biopsy sections were interpreted as adenoma of the bronchus. Pneumonectomy was attempted in 1944 but was abandoned because of the complete obliteration of the pleural space by extremely dense fibrous tissue. A month later, thorocoplasty and cauterly drainage of a large dilated bronchus was accomplished. The patient has a persistent bronchial fistula which drains purulent material, but she has no cough or hemoptysis unless the drainage tube becomes obstructed. She has been able to do all household tasks for the past three and one-half years. No further bronchoscopy has been done.

Pathology Only biopsy specimens could be studied but large pieces of tissue were examined (Fig 3). Microscopically the architecture was variable. At one extreme, well formed glandular structures separated by connective tissue trabecula were seen, while in other areas solid clusters of cells with only scattered septa were found. The cells were usually cuboidal to columnar with faint pink cytoplasm. The nuclei were round to oval with uniformly scattered fine chromatin material. No mitotic figures were seen.

The diagnosis in this patient is adenoma of the bronchus. She has had symptoms for 10 years but shows no evidence of any metastases from her primary tumor. Only biopsy specimens were obtained, and she obviously has residual tumor.

Case 6 S J This patient was a 63 year old nun who had been coughing for many years but particularly frequently during the past 10 weeks. Pain in the right chest, night sweats and anorexia were present, but at no time had she had hemoptysis. Roentgenograms revealed an atelec-

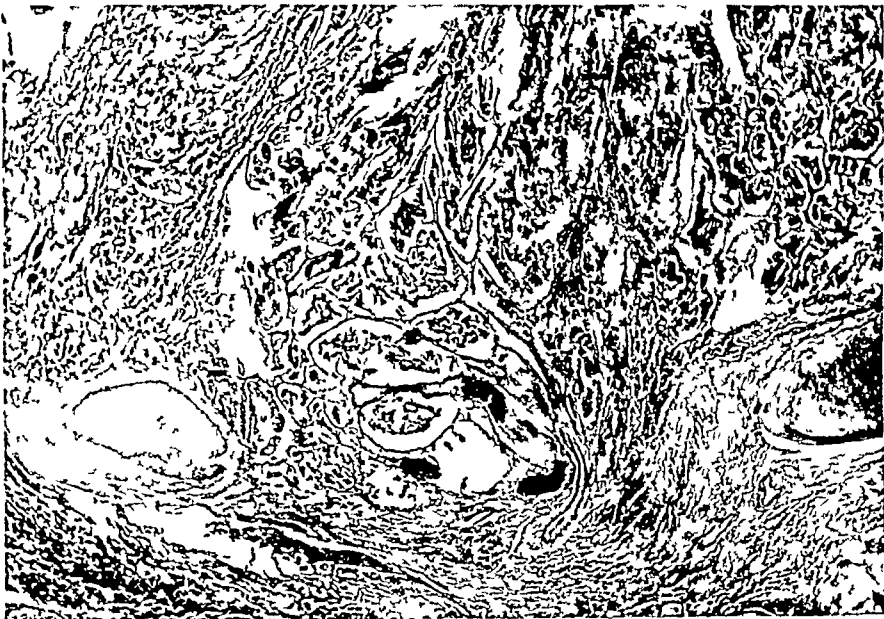


FIGURE 2, Case 5 (35X) Base of tumor. Note invasion of tumor into wall of the bronchus between the tips of the cartilage and the presence of a spicule of bone.

tatic shadow sharply outlining the right middle lobe. On bronchoscopic examination approximately 1 centimeter within the middle lobe orifice an obstruction was encountered from which tissue was obtained. The first diagnosis was carcinoma of the bronchus, and with that assumption, the right lung was removed in February 1946.

Pathology The tumor nodule was within the middle lobe orifice, it was 6-7 mm in diameter and attached over a mucosal surface of approximately 8 mm. The lung tissue distal to the tumor was atelectatic. Microscopically fine trabeculations of connective tissue separated clusters of cuboidal to columnar cells having eosinophilic cytoplasm and uniform vesicular nuclei. A glandular arrangement was frequently seen but no secretion was apparent in the spaces. There was no evidence of extension beyond the cartilaginous plates or invasion into the nearby lymph nodes. Final diagnosis was adenoma of the bronchus. The patient is living and well with no evidence of metastasis or recurrence.

Case 3 G.L. This patient is a 53 year old white male who complained chiefly of cough of at least five years' duration. Two years previously he had an attack of pneumonia associated with pleural fluid which was aspirated at another hospital. Shortly thereafter his first hemoptysis occurred. He had spells of coughing, fever, and expectoration of large quantities of pus shortly before admission followed by more bleeding. Roentgenograms of the chest revealed an atelectatic shadow corresponding to the left lower lobe. On bronchoscopy a tumor was found located just below the orifice of the left upper lobe obstructing the lower lobe bronchus. The biopsy was reported as adenoma of the bronchus. The patient had a lobectomy in December of 1946, and has been well since with no further pulmonary symptoms.

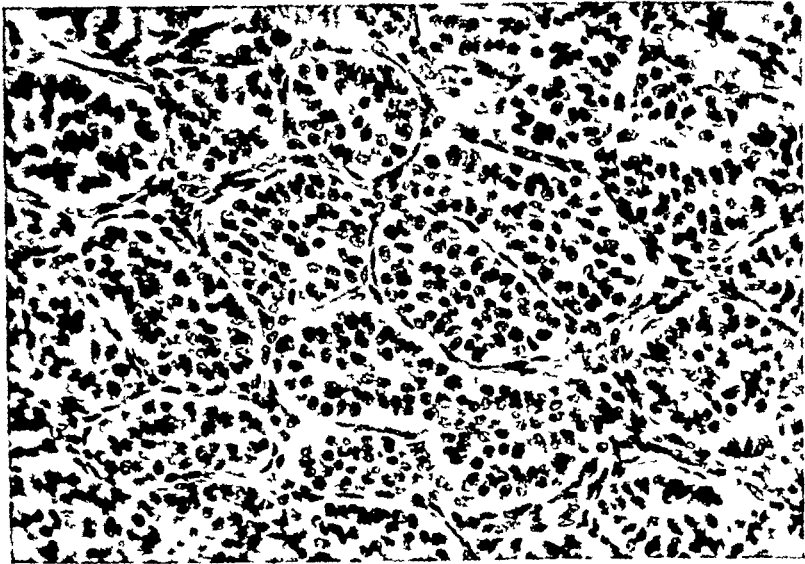


FIGURE 3 Case 13 (440X) Adenoma in which glandular structures are separated by thin collagenous tissue septa. Note cell and nuclear uniformity and the marked cellular hyperplasia which has resulted in the lumina being filled with cells.

Pathology A flat fleshy tumor measuring 1.2 centimeters in diameter was found just distal to the site of amputation. It involved an area of bronchial wall 8 mm in diameter, and the tumor extended through the wall in somewhat dumb-bell fashion so that a nodule of tumor measuring 6-8 mm in diameter was present beyond the bronchus. The distal lung tissue was solid and airless with fibrous tags on the pleural surfaces and dilated bronchi containing purulent secretion within the parenchyma. No tumor metastases were present in the lymph nodes. The microscopic pattern was one of solid clumps of cells separated by thin connective tissue septa (Fig. 4). The individual cells were cuboidal with eosinophilic cytoplasm and vesicular round nuclei. Little or no tendency to glandular formation was apparent. The final diagnosis was adenoma of the bronchus (Figure 4).

Case 14 R.H. This patient, a 49 year old white female, complained of cough of a year's duration and attacks of pleural pain. There was no previous hemoptysis. Roentgenograms had shown a density in the right lower lung. Because of a diagnosis of unresolved pneumonia, the patient had a bronchoscopic examination elsewhere which revealed a papillary tumor interpreted as adenoma. Bronchoscopy in 1942 revealed the tumor to be papillary in character and to originate at the entrance to the right lower lobe, immediately below the middle lobe orifice. The major portion of the tumor was removed with bronchoscopic forceps and by electrocoagulation and a small residual portion was removed similarly four months later. At least six subsequent examinations have been made and no tumor tissue has been found. The patient has been well, without symptoms for five years. Pathologic diagnosis was adenoma of the bronchus.

Pathology The variation in the microscopic picture is seen in figure

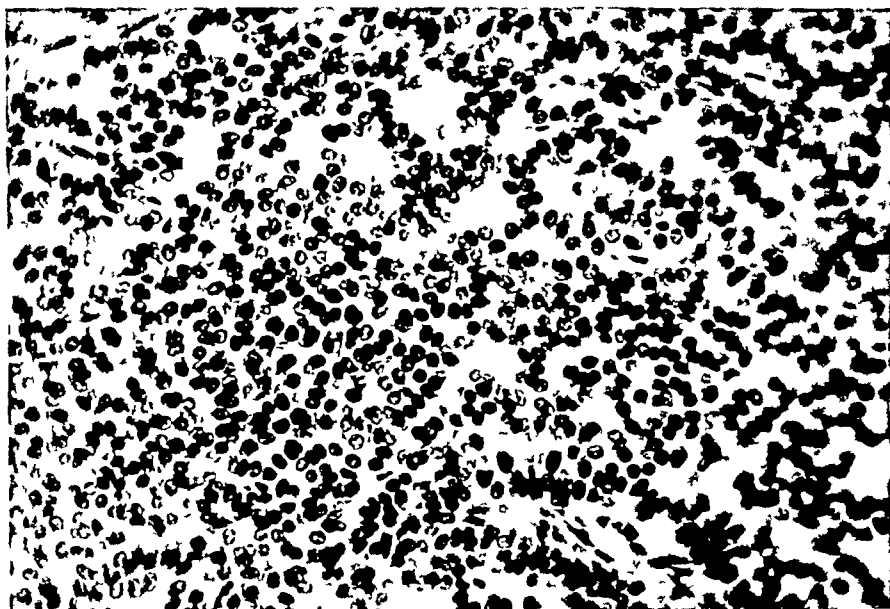


FIGURE 4 Case 3 (440X) Adenoma consisting of occasional acini but for the most part diffuse sheets of cells which still retain uniformity. Nuclei little and mitotic figures absent.

5 under $110\times$ magnification. On one side an anastomosing network of cells is found separated by connective tissue of varying dimensions often containing thin walled vessels. At the other margin, the cells are found scattered or in clusters. Glandular pattern is not well demonstrated. The individual cells, however, were cuboidal, eosinophilic and with little variation as to size, shape or staining. Although there is little tendency to form glands, the final histopathologic diagnosis is adenoma of the bronchus. It is made on the character of the individual cells. This variation in the microscopic picture in biopsy or surgical specimens is not uncommon, and careful study of the individual cells is of importance in establishing the final diagnosis (Fig. 6).

Case 11 C.H. This patient, a 50 year old white female, had symptoms of cough for five years, particularly severe in the past three to four months. The dyspnea was characterized by inability to completely force out air, and there had been some wheezing at times. Bronchoscopic examination revealed a round tumor occluding the left main bronchus, lying 15 cm. below the bifurcation of the trachea. A biopsy was interpreted as adenoma of the bronchus and in July, 1944 her left lung was removed. The tumor had infiltrated the wall of the bronchus making it friable, and as a result the bronchus tore during the procedure. A segment was removed above the line of defect and closure effected. The convalescence was uneventful and the patient remained symptom free for four years. In June, 1948 she was examined again because of gradually progressive dyspnea and a sudden change in voice. The left vocal cord was found to be paralyzed, the trachea compressed and the coryna markedly distorted. Irregular tissue removed from the entrance of the stump of the left main bronchus showed tissue similar to that found on the first bronchoscopic examination.



FIGURE 5 Case 14 ($110\times$) Adenoma consisting of anastomosing cords of cells forming false acini at one margin and solid sheets and clusters of cells in an adjacent area

Pathology Study of the resected lung showed that the segment of bronchus above the point of accidental rupture contained tumor tissue along 12 cm of its 28 cm length. The neoplasm elevated the bronchial mucosa for a distance of 8 mm and involved all but 2 mm of the circumference. The bronchus attached to the lung contained tumor extending into several of the smaller branches. The bronchi of the upper lobe were dilated and contained mucopus, and the parenchyma was firm and atelectatic. The lower lobe bronchi were slightly dilated. Microscopically the tumor was composed of clusters of epithelial cells in a rather dense stroma with little evidence of vascularity. There was great tendency to form glands of several layers' thickness and many of these contained pink or purple secretion. Frequently several glands were present in a cluster of cells, and in other instances the cell groups were solid. These clusters were seen to invade into the tissues beyond the cartilaginous plates. The individual cells were variable from columnar to cuboidal and the nuclei varied in size, shape and staining. The final diagnosis in this specimen was cylindroma of the bronchus (Fig 7).

Case 12 LM This patient was a 53 year old white female who complained of episodes of hemoptysis for 10 months and cough for four months. X-ray film of the chest demonstrated a partial atelectasis of the right lung. On bronchoscopic examination in January, 1941 a tumor was found partially filling the right main bronchus and extending to the coryna. A biopsy specimen was reported as bronchogenic adenocarcinoma.

Because of the extent of the tumor to involve the coryna, surgical removal was considered impossible, and the subsequent course of treatment was repeated bronchoscopic removal of tumor to maintain an airway into the right lung. Between these procedures the patient's



FIGURE 6, Case 1 (110X) Adenoma revealing characteristic acinar architecture but demonstrating clusters of cells invading adjacent collagenous tissue

clinical course was punctuated by episodes of hemorrhage and dyspnea. Eventually, after five years, the tumor grew into the trachea and serial chest x-rays showed nodular densities appearing in the left lung with gradual development of a complete atelectasis of the right. Because of the slow course of what was supposed to be a bronchogenic carcinoma, the biopsy specimens were reviewed. There was a variation of opinion among pathologists as to whether the lesion was an adenoma, a cylindroma, or a bronchogenic adeno-carcinoma. The patient finally expired due to a massive hemorrhage and asphyxia. This was five and one-half years after the tumor had been discovered.

Pathology At necropsy, there was complete atelectasis of the right lung with deviation of the mediastinum to the right side. The collapsed lung contained firm gray tumor which bulged into the trachea from the normal bronchial site, invaded the hilar lymph nodes and involved roughly 75 per cent of the lung parenchyma. At the periphery were six to eight solitary metastases, and in the opposite lung were more than a dozen discrete masses of tumor ranging from a few millimeters to centimeters in diameter. The left main bronchus contained a large amount of freshly clotted blood which was the cause of her sudden asphyxia. Metastatic lesions were seen in the kidney.

Microscopically the tumor was composed of varying sized clusters of cells either solid or forming one or more glandular spaces (Fig 8A). In some areas the stroma was largely replaced by broad sheets of cells with many glandular spaces containing pink or purple mucinous material while in others the thin stromal tissues formed branching networks around the cell groups. The individual cells were variable in size and usually contained only a small amount of cytoplasm. The nuclei were generally deep staining, occupied almost all of the cell space, and varied



FIGURE 7 Case 11 (110X) Cylindroma. The stroma is more dense and the acini are likened to cylinders frequently containing secretion and often having multi-layered cell walls.

in size and shape Mitotic figures could be seen but only very occasionally The microscopic appearance of the metastatic foci was the same as the primary The final diagnosis was cylindroma of the bronchus with metastases of hilar lymph nodes, contralateral lung and kidney (Fig 8B)

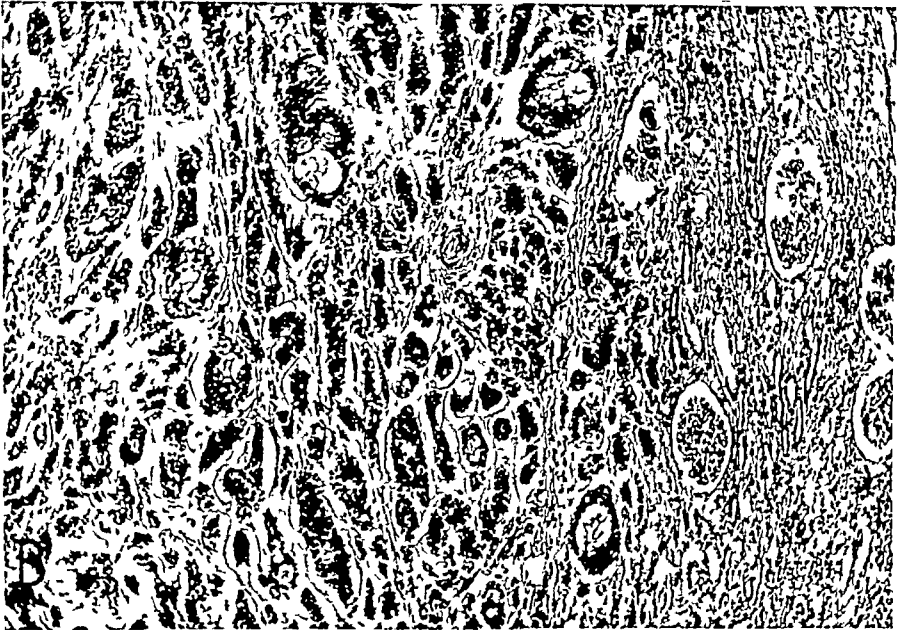
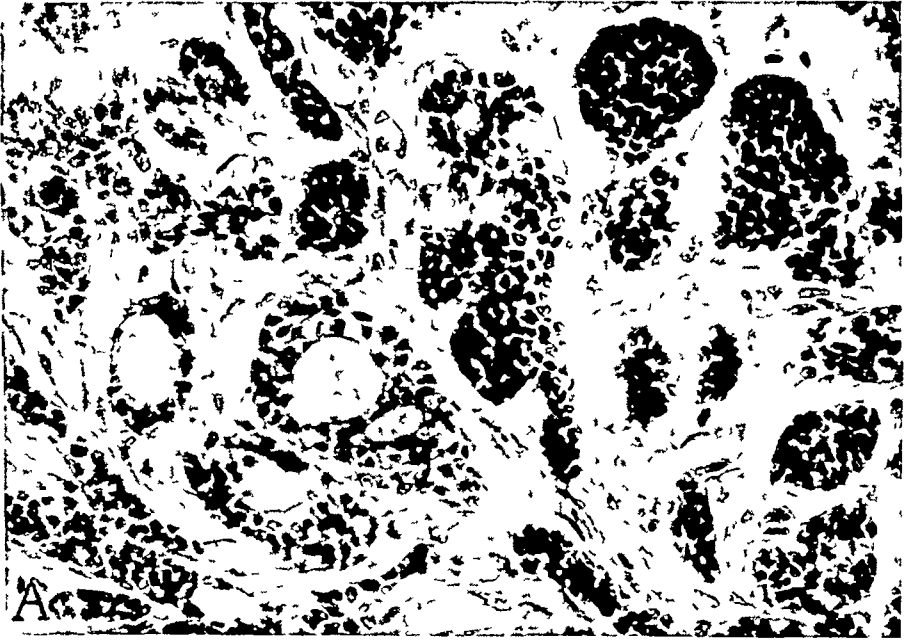


FIGURE 8A, Case 12 (440X) Cylindroma in which acini are single or multi-layered or solid masses of cells Note presence of secretion in many glandular spaces—FIGURE 8B Case 12 (110X) Kidney with cylindroma metastasis reduplicating histologic picture of primary lesion, Figure 8A

Discussions

Origin A brief review of Table 1 reveals that in every patient in this group, the neoplasm was found in a major bronchus. This same feature has been mentioned in most of the reported cases,¹⁻³ although, Maier and Fischer⁴ reported five cases of adenoma in each of which the tumor was found in a small branch bronchus and gave none of the usual symptoms of pulmonary suppuration. It is of interest to note that microscopic lesions strongly suggestive of adenoma have been seen in two of our patients not reported in this series. One of these lesions was found accidentally in a right lower lobe removed for bronchiectasis, the other in a lung removed at autopsy in an individual who died of arteriosclerotic heart disease. In each case, the lesion was remote from a large bronchus.

Heretofore, the origin of these tumors was considered by most physicians to be from the glands of the main large bronchi. On the other hand, Stout⁵ and Hamperl⁶ believe that adenomas arise from special cells called onkocytes. These can be seen best by special staining techniques and are found in the bronchial mucosa, and serous and mucinous glands. Womack and Graham,^{7,8} Harris⁹ and Albertini¹⁰ propose the theory of origin from embryonal bronchial buds. Harris studied serial sections of human embryos and further stresses the importance of the similarity between the haphazard arrangement of bronchial glandular elements in the embryos to the picture seen in adenomas. These authors also emphasize the frequency with which other tissues such as cartilage, bone, muscle, and fat occur in adenomas and believe this fact to be additional support of the theory that they derive their origin from embryonic bronchial buds.

From the studies of the cases in our series, we believe that the origin is most likely from either the serous or mucinous glands of the main bronchi.

Nomenclature Many different names have been proposed in the various series reported in the literature. Among them are "mixed tumors of the bronchus," "malignant adenoma of the bronchus," "benign glandular tumor of the bronchus," "carcinoid of the bronchus," "basal cell carcinoma of the bronchus," etc. Although "mixed tumor" is used because of the presence of other tissues, bone was seen in only two of our cases (No. 4 and No. 5) (Fig. 2). In these two cases the bone was not neoplastic tissue but developed as a result of metaplastic changes secondary to long standing infection. Case No. 4 in our series had a total pneumonectomy elsewhere, this case was reported by Mallory.¹¹ We agree with his interpretation that the presence of the bone tissue

in the tumor may be due to metaplasia associated with long standing pulmonary infection

"Malignant adenoma" is almost a paradoxical term Adams, Steiner and Block¹² have advocated it because in their series of five patients metastases were found in four "Carcinoid" has been proposed since the tumor has a resemblance to the peculiar argentaffin tumor of the appendix However, almost all cases fail to show silver granules In one of the cases in Holley's¹³ series, silver staining granules were found in biopsy tissue No special staining technique was carried out in our material

The term "basal cell" tumor of the bronchus is proposed because of the resemblance to certain skin tumors known as *epithelioma adenoides cysticum* which is considered a variety of basal cell carcinoma of the skin This term seems more fitting because of the clinical characteristics rather than the actual histopathologic picture

Lastly, Moersch, Tinney and McDonald^{14 15} have divided these tumors into the adenoma and cylindroma groups, stressing distinct differences as to histology and clinical course This division is a rational one "Adenoma of the bronchus" immediately suggests a specific type of bronchial tumor, although differences of opinion regarding many phases of this clinical entity do exist, these differences are becoming narrower The cylindroma is a distinct variant with clinical as well as pathological criteria that make it a separate entity

Symptomatology Tables II through IV summarize the main clinical features of adenomas and cylindromas as they occurred in the cases of this series A greater incidence in the female, with occurrence most frequently in the 30 to 40 year age group, and

TABLE II
SEX DISTRIBUTION

	Male	Female
Adenoma	6	14
Cylindroma	0	2

TABLE III
AGE DISTRIBUTION

	20-30 yrs	30-40 yrs	40-50 yrs	50-60 yrs	60 & over
Adenoma	2	10	4	3	1
Cylindroma	0	0	0	2	0

with hemoptysis occurring in at least 80 per cent of the patients is well in accord with other reports. It is worthwhile to correlate the pathologic changes with the symptoms most frequently found.

First, the prominent symptom of hemoptysis appears to be the result of the actual tumor architecture and blood supply. The photomicrographs readily reveal the small thin wall vessels that course between the glandular and cord-like elements. Trauma from coughing can easily disrupt the continuity of vessel walls with resulting hemoptysis. The other symptoms which develop

TABLE IV
INCIDENCE OF HEMOPTYSIS

	Present	Absent
Adenoma	15	5
Cylindroma	1	1

TABLE V
SUMMARY OF TREATMENT AND END RESULTS

ADENOMA

<i>Bronchoscopy,</i>			
Biopsy only			1
Complete removal	Living and well	Symptom free	5
Partial Removal,			
Improved			4
Died			0
<i>Surgical Resection,</i>			
Pneumonectomy,			
Living and well			4
Improved			1
Died			1
Lobectomy,			
Living and well			1
Improved			1
Died			1
Others,			
Improved			1**
<i>Total Cases</i>			20

CYLINDROMA

<i>Bronchoscopy,</i>		
Partial Removal,		
Died	1	
Pneumonectomy,		
Improved	1*	
<i>Total Cases</i>		2

*Case 11 Recent evidence of recurrence

**Case 13 Thoracotomy only Tumor still present

are related to the mechanical factors caused by bronchial obstruction. As the tumor grows into the lumen the passage of air currents over it is altered producing the wheeze so characteristic of the early stage of the symptoms. With more pronounced and finally complete obstruction, all exchange stops and the lung distal to the tumor becomes atelectatic. Varying degrees of bronchopulmonary suppuration may follow, leading to bronchiectasis or abscess or extension beyond the lung to involve the pleural space. Marked pleural reaction was present in four of the cases operated.

Pathology From the standpoint of gross pathology, the smooth, rounded, red appearance of the lesion seen bronchoscopically is quite characteristic and needs no further comment. Of the 10 patients operated, it was possible to study the surgical specimens in seven, the others having had their surgery elsewhere. Of the five surgical specimens which we have classified as adenoma, all had broad points of attachment such as described in cases No. 3 and No. 5. Occasionally there was extension of tumor through the wall in dumb-bell shape fashion. The gross and microscopic features of the two cases classified as cylindroma have already been described (Cases No. 11 and No. 12, Figs. 7 and 8).

From biopsy or surgical specimens, this series may be divided into two groups. Twenty cases were considered as adenoma and two as cylindroma. In reviewing the adenoma specimens, it was at once apparent that variation in the microscopic picture did exist. Moreover, in large biopsy specimens, variations were seen in the same slide. Figures 2 and 3 are both adenomas, yet Figure 2 demonstrates the lumina of the acinar spaces to be filled with cells. In another area of this particular specimen, solid sheets of cells were present with little or no dividing stroma. Figure 3 is a classical example of what is currently being accepted as an adenoma. Yet Figure 4 again demonstrates the diffuse cellular character which may be seen. In this patient, the tumor extended in a dumb-bell manner through the wall of the bronchus. Figure 5 is taken from Case No. 14. At this low power we again have an example of variation in the architecture in the same field. Of the five specimens obtained by pulmonary resection which allowed examination of the entire tumor, invasion by small clusters of cells into the deeper tissues of the bronchus was seen in four. Figure 6 under low power (Case No. 1) demonstrates this very well.

Only two cases in this series are classified as cylindroma (see abstracted cases 11 and 12). Microscopically the invasion was evident as clusters of tumor cells were found invading freely between the plates of bronchial cartilage. Figure 7 is a photomicrograph from the surgical specimen of case No. 12. Figure 8A and B are from the primary tumor in the lung and metastases

to the kidney respectively of the same case. This histologic pattern is accurately reproduced in the latter.

Despite the variation in the architectural arrangement of the *adenoma* group, the individual cells are very similar. Briefly, these cells are cuboidal to columnar, have a faint eosinophilic granular cytoplasm and round to oval nuclei. The chromatin network is usually fine and scattered. Mitoses are extremely rare. Even in those adenomas in which glandular spaces are almost totally lacking, it is difficult to find mitotic figures.

The *cylindroma* type, however, has a different type of cell and many times it is difficult to make out individual cell borders. The nuclei are more variable and the chromatin is more dense and stains more deeply. When a glandular pattern is observed in the adenoma group, seldom, if ever, is secretion found while in the cylindroma type a pink to purple mucin-like material can be seen. Comparison of the photomicrographs reveals the differences mentioned.

From the standpoint of pathology, it is valid to divide these tumors into the two types, since the cylindroma is an active, invading tumor in contradistinction to the adenoma. In one of the cylindromas distant metastases were observed. However, while tumors in the adenoma group also demonstrate small invading clusters of cells, distant metastases could not be demonstrated. In the two patients who came to necropsy, the *invasive* feature of the true adenoma is undeniable (See Figures 1 and 6).

Thus, the fundamental question may be raised as to whether these tumors should be considered benign or malignant. It is not necessary that the presence of metastases be a criterion of malignancy. For example, gliomas of the central nervous system do not metastasize but rightfully are considered malignant. Basal cell carcinomas of the skin are malignant tumors yet metastasis is uncommon. It is interesting that original diagnosis in early cases of various series reported was frequently bronchogenic carcinoma. The fact that the clinical course was so unlike bronchogenic carcinoma eventually led to re-evaluation, and accordingly the diagnosis was changed to adenoma. Likewise, in our series the diagnosis in early cases was carcinoma. The re-evaluation has led to the correct interpretation.

More recently, further classification is developing. Some writers in reviewing cases have realized that some classified as adenoma were different enough histologically as well as clinically. Holley¹³ divides the two into a carcinoid and mixed tumor type. We prefer to use the adenoma and cylindroma terms similar to the terminology suggested by Moersch, Tinney and McDonald.^{14, 15} The cases herein presented give further support that this distinction

is necessary since the cylindroma type is unquestionably a more invasive tumor

From the foregoing study and discussion of the cases herein presented, two statements may be made. First, these bronchial tumors represent a group entirely separate from bronchogenic carcinoma both from a pathologic and clinical standpoint. Second, it is further possible and desirable to subdivide the group and to recognize an adenoma and cylindroma type.

Treatment and Results

The therapeutic procedures available to the endoscopist or surgeon are numerous. Endoscopically the tumor may be resected by forceps removal or may be coagulated with the electrocoagulating bronchoscope.¹⁶ Large tumors obstructing major bronchi may be removed in massive sections through a coring technic¹⁷ of advancing the entire bronchoscope through the lesion into tumor-free bronchus beyond. This may be followed by electrocoagulation of residual tumor tags. The appreciable danger¹⁸ associated with such bronchoscopic procedures is the hemorrhage due to the well known vascularity of adenomas. It has been suggested that if bronchoscopic means of removal are to be used the tumor first be injected with a sclerosing agent or radon seeds to reduce the possibility of this complication.

The therapeutic procedures available to the surgeon are primarily lobectomy and pneumonectomy. Segmental lobectomy may be considered, but generally the tumor involves a bronchus leading to at least a whole lobe if not the entire lung. Bronchotomy with removal of a tumor with a section of the bronchus has been described for certain benign tumors, and this might be considered in rare cases of adenomas. Such a technic is valueless if the lung distal to the tumor is sufficiently involved in a suppurative process to necessitate its removal. It becomes necessary to employ other procedures discussed below at times when surgical exploration makes it apparent that lobectomy or pneumonectomy is not surgically feasible.

With the numerous bronchoscopic and surgical procedures available the following factors influence the choice of therapy. Immediate radical excision (pneumonectomy) is advocated if the tumor proves to be a cylindroma type. A variation of approach may be considered if the tumor proves to be adenomatous in character.

In this series of cases, bleeding associated with cautious forceps removal of tissue for biopsy became one of the criteria which determined whether further attempts to remove tissue would be made bronchoscopically or whether this method would be aban-

done immediately. Repeated attempts at endoscopic removal of a freely bleeding tumor will ultimately result in fatal hemorrhage. In only one case in this series radon seeds were injected into the tumor in an attempt to reduce hemorrhage prior to endoscopic removal. The procedure did not appear to influence bleeding.

The position of the tumor will in itself be an important factor influencing the choice of therapy. Upper lobe lesions as a rule cannot be completely removed through the bronchoscope because of their anatomically inaccessible position, unless, as occurred in one case in this series, the tumor lies in the orifice of an upper lobe bronchus. Tumors originating in the main bronchi or the lower lobe bronchi are easily accessible bronchoscopically and the re-establishment of bronchial continuity is therefore feasible and practical by this technique.

Another factor influencing the choice of therapy is the condition of the lung distal to the obstruction. If extensive pulmonary suppuration and irreversible parenchymal change have taken place which would of themselves necessitate a lobectomy or pneumonectomy, endoscopic attempts to remove the tumor are obviously of value only to enhance drainage prior to surgery.

Finally, the continuation of bronchoscopic tumor removal is dependent on the results being obtained. If the bronchus can be cleared by simple endoscopic removal during two or three sessions and checked from time to time, radical surgery hardly seems necessary. However, if there are rather regular recurrences, extirpation of the lobe or the lung is advocated.

Table V summarizes the treatment employed in this series. Of the 20 adenomas, 10 have been treated by bronchoscopic removal alone and 10 by external surgical approach. Of the 10 bronchoscopically treated patients, one had a biopsy only (This patient is the only one in the series not traceable). Five of the 10 are living and well, symptom free and with no evidence of residual tumor. Four are living and improved, with residual tumor but for the most part asymptomatic. There have been no deaths in this group.

Ten cases were treated surgically: seven by pneumonectomy and three by lobectomy. Of the seven pneumonectomies four are living and well. One operated elsewhere is improved but with surgical complications remaining. One is improved following attempted pneumonectomy, although it was not surgically feasible to remove all the tumor. One postoperative death following pneumonectomy was due to sudden development of tension pneumothorax and empyema. This case is discussed in detail above. Of the three lobectomies, one is living and well with no residual tumor. One is improved although the tumor was incompletely

removed This patient was operated elsewhere and it was the decision of the surgeon to do only a lobectomy rather than remove the entire lung due to circumstances at the time of the surgery The third lobectomy died postoperatively due to cardiac failure

The two cylindromas in this series were treated by opposite extremes of therapeutic possibilities This was due not to a desire to test either therapeutic procedure but to the factors inherent in the tumors themselves In the first patient, the tumor was considered surgically inoperable at the time the diagnosis was first established because of the invasion from the right bronchus into the trachea This patient lived five and one-half years because of frequent bronchoscopic removal of tumor tissue The second patient had a total pneumonectomy and remained well for four and one-half years without further therapy Recently she developed dyspnea and hoarseness, and examination has shown a paralysis of the left vocal cord and extensive mediastinal metastases with recurrence of the tumor in the bronchial stump

The results of treatment of this series correspond with those of other reports Both bronchoscopic and surgical measures were available and were used according to the indications and contraindications discussed

SUMMARY

Twenty cases of adenoma and two of cylindroma of the bronchus are presented and analyzed according to their history and clinical, x-ray and bronchoscopic findings The histopathology is discussed to emphasize the differentiation between adenomas and cylindromas The adenomas are considered as extremely slowly growing but invasive tumors, rather than metastasizing malignant neoplasms, whereas cylindromas meet all the criteria of malignant lesions

Choice of therapy was influenced by the location and histologic character of the lesion, the presence or absence of bronchopulmonary changes peripheral to the lesion, the degree of hemorrhage associated with the bronchoscopic procedures, and the response to endobronchial therapy Of the 20 cases of adenoma, 10 were treated by bronchoscopy alone and 10 by subsequent surgical procedures Of the former group (bronchoscopic), complete removal was effected in 5, of whom 4 are improved, and 1 was seen for biopsy only and has not been traceable Of the latter group (surgical), total pneumonectomy was performed in six cases, four are living and well, one improved, and one died postoperatively Lobectomy was performed in three cases, one is living and well, one improved, and one died postoperatively The 10th surgically

treated patient merely had a thoracotomy with cautery drainage, resection being impossible due to extensive adhesions. In the cylindroma group, one patient was treated bronchoscopically for 5½ years merely to keep the tracheal and bronchial airway open since the tumor had involved the entire right bronchus and invaded the trachea at the time of diagnosis. The second patient in this group was treated by immediate pneumonectomy but had a recurrence 5½ years later.

RESUMEN

Se presentan veinte casos de adenoma y dos de cilindroma bronquial y se analizan de acuerdo con su historia clínica, los rayos X y los hallazgos broncoscópicos. Se discute la histopatología para hacer resaltar la diferencia entre cilindromas y adenomas. Los adenomas son considerados como tumores extremadamente lentos para crecer, pero invasores más bien malignos y metastatizantes en tanto que los cilindromas reúnen todas las características de neoplasias malignas.

La elección de tratamiento fue influida por la ubicación y el carácter histológico, la presencia o ausencia de cambios broncopulmonares distales a la neoformación, el grado de hemorragia consecutivo a la broncoscopia y la respuesta al tratamiento endobronquial. De los 20 casos de adenoma, 10 fueron tratados por broncoscopia y 10 por subsecuentes procedimientos quirúrgicos. Del primer grupo (broncoscópico), se logró extirpación completa en 5, de los que 4 han mejorado y uno solo fue visto para biopsia y ahora se ha perdido de vista. Del segundo grupo (quirúrgico) se hizo neumonectomía total en 6 casos, cuatro están vivos y bien, uno mejorado y uno murió en el postoperatorio. Se hizo lobectomía en tres casos, uno está vivo y bien, uno mejoró y uno murió en el postoperatorio.

Al décimo caso, tratado quirúrgicamente, solamente se le hizo toracotomía con drenaje al cauterio, pues la resección fue imposible debido a adherencias muy extensas. En el grupo de cilindromas, un enfermo fue tratado por cinco años con broncoscopia solamente para mantener abierto el paso de aire a tráquea y bronquios, puesto que el tumor había invadido completamente el bronquio derecho y la tráquea cuando se hizo el diagnóstico. El segundo enfermo de este grupo fue tratado con neumonectomía inmediata, pero tuvo una recurrencia a los cinco y medio años más tarde.

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D i s c u s s i o n

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I was glad to read in the abstract of Dr Holinger's paper that the emphasis was put on pathology, because I believe that the crux of the confusion in this subject of benign adenoma and similar tumors lies in the pathology, the necessity for sorting out several different types, at least these two, particularly differentiating the adenoma from the cylindroma. That is a step in the right direction, taken by Van Hazel, Holinger and Jenik. I had the privilege of hearing a most interesting discussion at the Thoracic Surgeons' meeting in Quebec recently, papers by Goldman of San Francisco and Neuhof and Rabin of New York, and then a lot of discussion. Neuhof and Rabin presented 65 cases and they made a particular point of restricting their list to adenoma cases, and stated that they were leaving out cylindromas, mixed tumors and several others that they mentioned. In the discussion they were criticized for leaving out these cases,

by some who do not recognize the differential histopathologic diagnosis

It has been our contention that the typical adenoma has no inherent tendency to become malignant. We do not say that none become malignant. We of course insist that the low grade character of the malignant cylindromas is important in deciding what treatment should be given. We have been increasingly impressed with the importance of taking into consideration the extrabronchial portion of the growth, as Dr. Holinger has well demonstrated in some of his sections. This is important, not so much from the point of view of further extension or metastasis, but because of bronchial compression by the extra-bronchial portion of the growth. There is one fact that stands out clearly in our minds, namely, that these cases should be individualized as to treatment. They should not be automatically subjected to lung resection as a carcinoma should.

We presented a report of 20 cases of adenoma in 1944 at a meeting of the Thoracic Surgeons, subsequently published in the Journal of Thoracic Surgery in April, 1945. Since then we have had 11 cases. Of the first 20, three were treated surgically, two by lobectomy and one by pneumonectomy, 17 were treated bronchoscopically. Of the 11 recent cases, three were treated by surgery and eight bronchoscopically. Thus there were 31 cases, seven treated surgically and 23 bronchoscopically.

Closing Remarks

Robert J. Jensik, M.D., Chicago, Illinois. We hope to add something to unequivocally establish these lesions as definite entities. I was pleased to see that the first two photomicrographs shown by Dr. Jackson were classified as cylindromas, because we feel strongly on that point, that this type must be separated from the adenomas. We are not original in this observation because others, including the Rochester group, have emphasized this differentiation.

We believe that the cylindroma types are certainly more invasive, and as you saw in one case in our series, there were definite distant metastases. Reviewing the histopathology, it is important to stress that cylindromas practically all have some evidence of secretion in the glandular forms that are present, whereas in the adenoma types we seldom see that. In adenomas we may see piling up of cells and obliteration of glandular pattern, but there is not criteria enough to say that malignant degeneration has occurred. In one of our cases the course has been at least eight years and yet there is no evidence of any distant metastasis and the patient is living and well.

As to whether they are benign or malignant, I think we might avoid that issue by saying that we should consider even adenomas invasive but with nowhere near the invasive tendency of cylindromas. We believe that since distant metastases are so uncommon in the adenomas one is not justified in saying the tumors must be considered benign. After all, such tumors as gliomas occurring in the central nervous system, or basal cell tumors of the skin, are considered malignant, yet metastases are rare.

Biochemical Studies in Cancer Diagnosis*

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In 1944 Savignac et al¹ reported that serum samples from patients with malignant disease exhibited a decreased ability to reduce methylene blue solutions. Using a technique which varied somewhat from that of Savignac, my own studies appeared to corroborate the essential validity of his observation.^{2,3} This paper will deal with studies of the reducing power of plasma as well as investigations on the heat sensitivity of plasma of patients with and without malignant disease.

The reducing power is measured by the ability of a plasma sample to decolorize a standard amount of methylene blue. The exact procedure consists in mixing 1 cc of plasma with 0.2 cc of 0.15 per cent aqueous solution of methylene blue in a Wasserman tube. The tube is then immersed in a boiling water bath until complete decolorization of the dye has occurred. In a study of more than 1,000 plasma samples from presumably healthy individuals, a characteristic distribution curve was obtained, the peak of which lies between 8 and 8.5 minutes. The upper limit of the curve is found at 10.5 minutes. This is at variance with similar studies of plasma samples from individuals with a wide variety of malignant disease. Here the reducing time values are more prolonged, and in some cases it may require more than 20 minutes to bring about complete reduction of the dye. This may be seen by the percentage of cases having reducing time values of 11 minutes or more, viz., carcinoma of the breast 40 per cent, carcinoma of the lung 73 per cent, carcinoma of the cervix 59 per cent, carcinoma of the colon 68 per cent.

Since there is a decided overlap of values in the time range of 9.0 minutes to 10.5 minutes, a second reducing power technique is employed when such time values are encountered. This procedure employs a 0.1 per cent brilliant cresyl blue in place of the methylene blue. After a 10-minute immersion in the boiling water bath, the tube is removed, cooled, and the color noted. In general, two main types of reactions are found: (1) complete reduction of the dye, resulting in a greyish-white coagulum, and (2) incomplete reduction of the dye, leaving a lavender-colored coagulum.

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The former reaction is obtained in testing plasma samples from healthy individuals, while the latter is found in a majority of patients with malignant neoplasia. In analyzing the reducing power values obtained by these techniques, it was assumed that all methylene blue reducing times of 85 minutes or less were normal values. All reducing times of 110 minutes were abnormally high, while reducing times falling between 90 minutes and 105 minutes were evaluated on the basis of the brilliant cresyl blue reaction. An incomplete brilliant cresyl blue reduction in such cases was considered to be evidence of a decreased reducing power, while a complete reduction was indicative of a reducing power within normal limits. The use of these criteria indicated a decreased reducing power in approximately 75 per cent of a series of 600 cases of diverse forms of malignant neoplasia, while no such decrease in reducing power was found in approximately 2,000 samples from healthy individuals. Most common diseases and benign tumors gave reactions similar to the control group. This was not the case in samples of tuberculosis, rheumatic fever, cirrhosis, and in gravid females. This would indicate that the alterations in reducing power, while seemingly associated with the presence of malignancy, is not specific for it.

The relation between the presence of a malignant growth and a decreased reducing power may also be observed by following patients who have received therapy, since the fluctuations in the reducing power in such patients is particularly interesting from the prognostic standpoint, as it provides an objective means of following the effects of the therapeutic procedure. Thus, variations have been seen after adequate therapy both in carcinoma and sarcoma wherein the therapy was radiation or surgery. It may be said, therefore, that while some cancer cases may exhibit normal plasma reducing times although they still harbor foci of malignant neoplasia, the persistence of an elevated reducing time is extremely strong evidence that all such foci have not been eradicated.

The mechanism of this change in reducing power in association with the presence of malignant neoplasia appears to be part of a systemic effect on protein metabolism. The previous studies by Savignac et al appeared to implicate the albumin fraction as the principal plasma component responsible for the reduction of the dye. My studies suggest that the -SH group of a protein component of the plasma, most probably albumin, is responsible for the reducing power as measured by the technique described.

In an attempt to evaluate the sulfhydryl group and the reduction of methylene blue, a study was undertaken with various compounds of known -SH and -S-S- structures⁴. Glutathione,

cysteine hydrochloride, and methionine were made up in equimolar solutions (0.0325 M) in distilled water. One cc of the glutathione solution was added to 0.2 cc of 0.13 per cent methylene blue solution. In a similar manner, the dye was added to 1 cc samples of the cysteine and methionine solutions. The tubes were then immersed in a boiling water bath and observed for time of complete decolorization. The tube containing methionine and methylene blue failed to show any change in color in spite of continued boiling for one and a half hours. On the other hand, complete decolorization was noted in the tubes containing cysteine HCl and glutathione in 60 and 15 minutes respectively. The reduction of methylene blue by cysteine and glutathione and not by methionine is an indication that in these compounds at least a free -SH bond is required. The more prolonged time for glutathione (15 minutes) as compared with cysteine HCl (6 minutes) would seem to indicate that the availability or reactivity of the -SH bond may be altered by its location in the molecule. Thus, in cysteine the -SH is terminal and presumably unhindered in its activity. In the case of the glutathione, the internal location of the -SH bond seems to decrease its reactivity. The reversible decrease in the reducing power of plasma associated with malignant neoplastic disease might be explained on the basis of changes in the spatial configuration of the albumin molecule. Such changes would be readily reversible and would not necessitate changes in amount of total proteins or -SH bonds. This is of importance since the observed decrease in reducing power is not correlated with changes in the concentration of the plasma proteins. Thus it appears that the reduction of methylene blue by plasma in the technique described is a measure of the reactivity or appearance of the reducing groups rather than a measure of the total number of such groups potentially available.⁵

While the presence of malignant disease is associated with a deficiency in albumin fabrication as evidenced by a lowering of the reducing power and often times a lowering of the serum albumin, the fibrinogen concentration tends to undergo elevation. This finding, reported by various investigators and corroborated in our own studies, indicates that the various protein components of the plasma are influenced differently by the presence of malignant disease. The exact significance of this difference is not clear, but it should be remembered that while albumin production appears to be a function of the liver parenchyma, this is not so for fibrinogen which more probably arises in the reticulo-endothelial system.

When plasma samples from individuals with and without malignant disease were exposed to a standard amount of heat, it

was noted that the former group tended to show a greater degree of turbidity.⁶ The procedure employed is as follows (1) 1 cc of plasma is placed in a Klett colorimeter tube and diluted to the 5 cc mark, (2) a reading of the light transmission is taken in the colorimeter, (3) the tube is immersed in a boiling water bath for exactly 10 seconds, (4) after cooling and drying the tube, a second reading of the light transmission is taken

The difference between the first and second readings is a measure of the coagulation or turbidity production and has been termed the coagulation value. When the values of plasma samples from healthy individuals were plotted, a peak was found at a value of 48, while less than 2 per cent of the cases extend beyond 82.

This was quite at variance with the results obtained when plasma samples of cancer patients were tested, since more than 60 per cent of the cases were found to have coagulation values of 80 or above. In view of the small percentages of controls with coagulation values above 79, it was arbitrarily decided to adopt a coagulation value of 80 or above as suggestive of the presence of malignant neoplasia. In a series of 199 cases of diverse cancer types, the mean of the coagulation values was 99.

It should be mentioned that the coagulation values obtained will vary somewhat when different colorimeters are used. Therefore, it is advisable for each laboratory to establish the normal limits for its own machine. When this is done, the values obtained with the plasma of cancer patients will show the same type of variation as reported here.

In a similar study of plasma samples from patients with non-neoplastic disease, it was found that while most of the common diseases did not cause alterations in the coagulation values, rheumatic fever, tuberculosis, and pregnancy yielded reactions which in some cases were indistinguishable from those of cancer patients. These findings indicate that the specificity of these studies is not absolute, a fact of extreme importance in the application of these findings to clinical problems.

In general, it may be said that benign tumors gave reactions similar to the control group.

As with the reducing time studies, adequate therapeutic procedures were followed by a return to normal of the coagulation values of cancer patients. These variations are well illustrated in a case of Hodgkins Disease that underwent several remissions and exacerbations. Fluctuations from values of 155 to 45 occurred as the patient went from an active state to one of clinical remission. With a recurrence of activity, the coagulation value rose from 172, only to fall to 55 as another remission was induced.

Chemical investigation of the basis of these changes indicated

that it is related to the fibrinogen concentration. Thus, similar heating of serum samples failed to induce a turbidity, and parallel determinations of fibrinogen and coagulation values revealed a correlation between the two. Since individual cases were encountered wherein the fibrinogen concentrations were the same but wide divergencies were noted in the coagulation values, it would appear that some other factor or factors are involved in addition to the fibrinogen concentration.

The use of the reducing power and coagulation techniques in combination revealed that the diagnostic accuracy could be greatly increased. Thus, cancer was considered to be present when a positive reaction was obtained with either or both tests. By the use of these criteria, cancer was identified in approximately 87 per cent of a series of 194 cancer cases of diverse types. Eighty-five per cent of the cases were identified by the use of the methylene blue and coagulation techniques without recourse to the brilliant cresyl blue procedure. Examples of the diagnostic accuracy in various common types of malignant growths may be found in the accompanying table. Here the diagnostic accuracy of the reducing power technique is compared with that obtained by utilizing both procedures.

It will be evident that while plasma samples from cancer patients do not always give malignant reactions with both the coagulation and reducing power studies, in most cases one or the other was positive. The high degree of accuracy in the identification of plasma samples from cancer patients warrants further

DIAGNOSTIC ACCURACY

CANCER	REDUCING POWER		COMBINED METHOD	
	Cases	Per cent	Cases	Per cent
Breast	61	66	34	89
Cervix	46	87	15	94
Colon	44	82	13	93
Fundus	21	62	12	88
Hodgkins	21	91	12	88
Lung	38	90	14	93
Lymphosarcoma	22	82	10	70
Prostate	14	93	4	100
Rectum	18	100	9	100
Sarcoma	15	87	6	100
Stomach	40	88	10	90

study of these tests of their value as a screening method for cancer. It should be emphasized, however, that similar reactions were also obtained in certain non-neoplastic conditions, and that approximately 10 per cent of the cancer patients tested were not identified by these methods. It is therefore important that these data should not be used indiscriminately. It is only with due regard for its limitations that it may be applied as an aid in the diagnosis and follow-up of cancer cases.

Finally, it should be pointed out that these observations add to the growing data on the systemic alterations in the tumor host and strengthen the concept that cancer is a systemic disease whose local manifestations may vary but whose presence is associated with a surprising uniformity of body milieu.

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D I S C U S S I O N

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At the Methodist Hospital in Brooklyn we have done about 400 of the reducing power tests, but none of the coagulation studies. In this discussion only the malignancies proved by autopsy, biopsy or operation will be presented, as Dr. Black has already given the controls on the normals.

In our group of malignancies we had 47 positive tests, of these, 41 were different types of carcinoma, 5 were lymphomas such as Hodgkins' disease and lymphosarcoma, and one was an acute leukemia. We had 15 negative tests in later proved malignancies. As in Dr. Black's series, we had a high percentage of cancer of the breast with five negative tests. There were five of the digestive

system, two pancreas, one stomach, and two of the colon. Of the lungs we had two negative tests, of the uterus one, of the ovary one and of bone one. This gives us a false negative percentage of 24 per cent.

In our entire group of positive tests there were 47 carcinomas. We also had the non-neoplastic conditions which we know will give a positive reaction that we can eliminate, such as newborns, 13, 100 per cent positive, penicillin therapy, 7, low plasma protein, 4 (below 5), and the last trimester of pregnancy, 3. Of the unknown positives we have 18.

To sum up the positive tests, give us carcinoma, 47, non-neoplastic conditions which we eliminated in the calculations, 27, and unknown causes, 18. This is a 73 per cent accuracy, which is fairly close to Dr. Black's 79 per cent.

In a breakdown of the false positives we had three cases of pernicious anemia with one death and no autopsy, two with fever of undetermined origin, accompanied with weight loss and still undiagnosed, three with gastrointestinal defects shown by x-ray, two of whom refused surgery, two cases of vaginal bleeding with negative biopsy, one case of ulcerative colitis, one case of thyrotoxicosis and two cases with symptoms of spinal cord pressure. Incidentally, one of these last-named has since been diagnosed as carcinoma of the prostate with metastasis. There was one case of anuresis in an eight year old child. This boy was given a thorough examination from every conceivable angle and no malignancy was found, though he had a consistently positive test. One case of myocardial infarct was not thoroughly investigated because of his serious condition. One gastric ulcer and one case of appendicitis also had positive tests.

Thus, we have done 400 tests for diagnostic purposes and have found 27 per cent false positives and 24 per cent false negatives. The test is 75 to 80 per cent accurate and we believe it worth while.

Closing Remarks

Maurice M. Black, M.D., Brooklyn, New York. There are some additional points that I might make. In addition to Dr. Morris' repetition of the work, I have also received other reports from various parts of the country. While as yet no series comparable to my own has been accumulated, more than 500 cases have been done in various laboratories, and I think it is fair to say that in general the results are quite similar to my report today. I concur in the instances of false positive results that Dr. Morris has pointed out. These are pregnancy, tuberculosis, active rheumatic fever, and marked hypoproteinemia. Similar false values may also be obtained in patients who are receiving penicillin treatment.

In general, these sources of error may usually be eliminated in the differential diagnosis. While additional study and confirmation are greatly to be desired, the techniques of the test are simple, and if the dyes are correctly calibrated and normal distribution curves established, there appears to be no reason why it cannot be used to advantage.

Acute Fatal Asphyxia Due to Aortic Aneurysm in Patient with Four Saccular Aneurysms of Thoracic Aorta Case Report*

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Acute asphyxiation as the cause of death in patients with aneurysm of the thoracic aorta is rare Ficarra,¹ in reporting a case with chronic compression of the trachea and right lung by an aneurysm of the ascending aorta, with death attributed to asphyxia resulting from chronic ischemic and anoxic anoxia, stated that "clinical and pathological literature on aneurysms fail to report any instance of asphyxia due to aortic aneurysms" Pernet² reported an instance of mechanical asphyxia due to gigantic aneurysm No other reference to acute asphyxiation has been encountered, although it is well known that mechanical pressure on the trachea and resultant respiratory difficulties are common in aneurysm of the thoracic aorta

Compression of the trachea by aortic aneurysm is most apt to occur when the aneurysm is situated in the transverse portion of the arch Lucke and Rea³ found compression of the trachea by two of 23 aneurysms at the junction of the ascending and transverse arch, and by five of 46 aneurysms of the transverse arch Keefer and Mallory⁴ state that tracheal compression usually results from pressure by aneurysm of the transverse arch or of the innominate artery

In cases of aneurysm of the ascending or transverse arch, Kampmeier⁵ found dyspnea to occur in 65 per cent and to be due most often to tracheal, bronchial, or pulmonary compression Boyd⁶ found dyspnea reported as the first or chief complaint in 31 per cent of cases of aneurysm of the thoracic aorta, and that more severe and steadily increasing dyspnea resulted from pressure on the trachea or large bronchi Several authors⁵⁻⁷ refer to a paroxysmal type of dyspnea, of unknown causation, but rarely seen in the absence of pressure on the trachea or large bronchi Changes in posture may precipitate a feeling of suffocation

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Kampmeier⁵ noted respiratory stridor in 11.7 per cent, and "choking spells" in 7.3 per cent of 205 patients with aneurysm of the transverse arch, such findings were much less frequent in cases with aneurysm of the ascending or descending arch. Of 247 patients with thoracic aortic aneurysm who died, he found 46 (18 per cent) died of respiratory obstruction. Keefer and Mallory⁴ mention that gradual suffocation may result from retention of tracheal and bronchial secretions. None of these writers makes mention of acute asphyxiation, as was dramatically observed in the case to be described.

The occurrence of multiple saccular aneurysms of the thoracic aorta is not infrequent, but the precise incidence cannot be determined from the data in the literature. Paullin and Minnich⁸ state that multiple aneurysms are fairly frequent, there being one fairly large saccular dilatation accompanied by many smaller ones. Wilburne and Taylor⁹ reported two patients who had three and one patient who had four aneurysms of the thoracic aorta. Lucke and Rea¹⁰ in a study of 268 necropsied cases with aneurysm, found multiple aneurysms (chiefly of the aorta, but occasionally an aortic aneurysm associated with aneurysm of one of the aortic branches) in 53 (19.7 per cent). In a more detailed study,³ but where the data given do not permit exact analysis, they indicate that at least one patient had three or more aneurysms. The figures of Colt,¹¹ which may be weighted because they were based in large part on published case reports, reveal an incidence of 57 cases (10 per cent) of multiple aneurysms among 575 patients with thoracic saccular aortic aneurysm, two aneurysms being present in 43 cases, three in seven, four aneurysms in four, and more than four in three patients. Kampmeier⁵ found 23 cases (3.6 per cent) with two or more sacs among 633 patients with aneurysm of the thoracic aorta, and at autopsy found five cases with two sacs and three with three aneurysms.

According to Stokes and associates,¹² small sacculations and finger aneurysms result from localized bulging at spots weakened by fibrosis due to inflammatory changes around the vasa vasorum. In cases of aneurysm, the systolic blood pressure tends to be low and the diastolic high. An intact aortic valve, by permitting a constant and even pressure on the aortic wall, favors the production of aneurysmal dilatation, while the development of aortic regurgitation tends to protect against the formation of aneurysm. Kampmeier⁵ states that hypertension, in the absence of aortic insufficiency, may aggravate the tendency to saccular dilatation.

The present report describes a patient who died of acute asphyxia when an aortic aneurysm suddenly occluded the tracheal

lumen This occlusion was observed bronchoscopically, yet at necropsy the tracheal lumen, though narrowed, was not occluded, suggesting that the tracheal obstruction during life was due to dynamic dilatation of the aneurysmal sac An incidental finding was the presence of three smaller aneurysms of the thoracic aorta

CASE REPORT

A 56 year old farmer entered the Veterans Administration Hospital, Aspinwall, Pennsylvania on the evening of August 6, 1947 He complained of dyspnea of one year's duration, most intense in the last three months, associated with progressively severe hoarseness of six months' duration and a marked cough He slept on two pillows and had experienced several episodes of nocturnal paroxysmal dyspnea His weight had declined from 135 lbs to 110 lbs There was no chest or back pain and no edema or palpitation Syphilis was denied by name and symptoms

On examination, the patient revealed evidence of recent weight loss He was slightly dyspneic and orthopneic at rest and extremely hoarse His cough was of metallic, rasping quality The neck veins were slightly distended The pupils were irregular and unequal but reacted to light The fundi could not be examined The trachea lay in the midline The point of maximum cardiac impulse was felt in the sixth interspace within the midclavicular line Dullness to percussion extended beyond the sternum in the left second interspace Grade IV systolic and diastolic, high pitched aortic murmurs were heard over the entire precordium A Duroziez murmur and pistol shot sound were heard over the femoral artery Marked capillary pulsation was present in the nail beds The blood pressure was 120/40 No pulsus alternans or gallop rhythm was present The lungs were hyperresonant and coarse bronchial rales were heard bilaterally The liver extended one fingerbreadth below the costal margin but was nontender The peripheral vessels appeared thickened and tortuous The knee jerks and ankle jerks could not be elicited No penile scar was apparent There was no edema

Laboratory Data The blood Kahn and Wassermann tests were positive The blood count revealed 3,190,000 red blood cells and 18,400 white blood cells per cu mm (neutrophils 84 per cent lymphocytes 16 per cent) hemoglobin 10 gm per 100 cc The urine contained a faint trace of albumin, frequent white blood cells one to two red blood cells per h p f, and rare granular casts the specific gravity was 1.021

On the day following admission while drinking through a straw the patient suddenly gagged or choked Following this he became extremely cyanotic, but the pulse remained of good volume at a rate of 80 per minute There was suprasternal retraction and the patient was using his accessory muscles of respiration The breath sounds were markedly depressed in all lung fields The initial clinical impression was tracheal obstruction An endotracheal tube was inserted and suction yielded considerable quantities of clear mucus without foreign material The vocal cords appeared grossly normal One hundred per cent oxygen was administered by mask with slight decrease in cyanosis The blood pressure was 240/69 The endotracheal tube remained in situ for approximately one-half hour during which time the patient appeared somewhat less dyspneic After removal of the tube intensification of the cyanosis ensued Questioning of the patient at this point revealed that he had

experienced one previous similar episode. A chest x-ray film showed cardiac enlargement, and dilatation of the aorta compatible with aneurysm. The respiratory obstruction progressed relentlessly as evidenced by increasing sternal retraction and the use of all accessory muscles of respiration. The patient appeared to be in extremis, and emergency bronchoscopic examination was performed. The trachea was seen to be markedly deviated to the right and almost completely occluded at its lower end by an extrinsic pulsating mass, believed to be an aneurysm. Marked pulsation of the aorta was transmitted to the bronchoscope. The patient became semicomatose and remained so until his demise three hours after the onset of the acute episode. No morphine had been administered.

Necropsy Findings The necropsy was performed five hours after death. The relevant findings were as follows. The pupils were round, but unequal, the right measuring three mm, the left four mm in diameter. The trachea appeared slightly deviated to the right on palpation. The skull and its contents appeared normal. Both lungs were wet, the left weighing 550 gm, the right 600 gm. The left lower and right upper lobes presented irregular purplish-red areas of doughy consistency. There was no evidence of foreign matter in the tracheobronchial tree.

The heart was hypertrophied, weighing 500 gm. The left ventricular wall measured 20-22 mm in thickness, the right five mm. The aortic valve revealed slight cord-like thickening of the free edge of the posterior cusp, the commissures being widened to two mm. The valve circumferences were as follows: TV 13 cm, PV 7 cm, MV 10 cm, AV 8 cm.



FIGURE 1 The aneurysm impinging on the trachea lies opposite the origin of the great vessels. The arrow on the right lies in the opening of a second sac. The other arrow points to the tiny third sac. The fourth aneurysm lies to the right of the upper arrow.

Thickened, puckered intima of the sinuses of Valsalva produced moderate narrowing of the coronary ostia. The branches of the coronary arteries were widely patent, however, the left anterior descending branch showed a few small, yellow intimal plaques.

The thoracic aorta was thickened, inelastic, and widened, measuring 8 cm in diameter in its ascending portion. The intima of the aorta down to the level of the renal artery was roughened by innumerable flat, yellow and grey-white plaques, between which the surface showed pitting and prominent linear and transverse wrinkling, giving a characteristic tree bark appearance. A remarkable feature of the aorta was the presence of four saccular aneurysms, three juxtaposed in the transverse arch, and one lying in the upper descending aorta (Fig 1). The most proximal was situated on the posterior surface of the aorta opposite the origin of the left subclavian artery. The opening presented a rolled edge and measured 20 x 20 cm in diameter. The sac ballooned to a maximal diameter of 40 cm and a depth of 30 cm, and was lined by laminated clot. This aneurysm was firmly adherent to the left bronchus and the left anterolateral surface of the trachea, into which it bulged about 0.6 cm. A second and smaller aneurysm lay adjacent to and slightly distal to the first sac, their orifices being separated by only 0.2 cm of ragged intima. This sac measured 15 x 15 cm in diameter, 0.8 cm in depth, and did not balloon. Its wall consisted merely of clot and thin adventitia. Above, about 0.4 cm anterior to, and at a level between the first two aneurysms, there was a tiny third aneurysm, measuring 0.4 x 0.4 cm in diameter and 0.5 cm in depth, its base was composed of clot. In the lateral aspect of the upper descending aorta, a fourth saccular aneurysm was found, slightly adherent to the anterolateral surface of the esophagus. The opening measured 10 x 10 cm in diameter, and the sac ballooned to a maximal diameter of 20 cm, and a depth of 0.7 cm. Its base consisted only of laminated clot. No hemorrhage had occurred from any of the aneurysms.

The liver showed moderate congestion. Both kidneys presented adherent capsules and cortical scarring. The second to sixth thoracic vertebrae, inclusive, were eroded along their left anterior surfaces. This erosion bore no close relation to any of the aneurysms and could not be attributed to them.

Microscopic Findings

Lung There was patchy bronchopneumonia.

Trachea There was partial ulceration of the epithelium and diffuse infiltration of the immediately underlying lamina propria by many polymorphonuclear leukocytes. The interstitial tissue of the mucous glands was heavily infiltrated by great numbers of plasma cells and lymphocytes, and a small circumscribed area of subepithelial necrosis was evident. The cartilage bars were partially ossified, and their outer surfaces broken. Multinucleated giant cells, large numbers of plasma cells and lymphocytes surrounded these fragments. Beyond the cartilage an organizing clot lay upon the necrotic and partially fibrosed wall of the adherent aorta. The small arteries of the tracheal wall showed fairly marked intimal thickening.

Aorta The media showed marked disorganization and presented areas of necrosis with disruption of the elastic fibers. Near these areas and throughout the media and adventitia the vasa vasorum were surrounded by masses of plasma cells and lymphocytes. Several of these vessels pene-

trated to the intima, which was irregularly thickened by hyaline fibrosis in which were areas of calcification and atheronecrosis

Kidney The picture was that of arterial nephrosclerosis

Final Principal Diagnoses (1) Asphyxia, acute, due to partial occlusion of trachea by aneurysm (2) Aortitis, syphilitic, with insufficiency of aortic valve (3) Aneurysms, syphilitic, multiple (four), thoracic aorta (4) Tracheitis, acute and chronic (5) Erosion, thoracic vertebrae (6) Hypertrophy, heart (7) Edema and congestion, lungs (8) Bronchopneumonia, acute, bilateral (9) Nephrosclerosis, arterial type

Comment

Since at necropsy the tracheal lumen appeared adequate as an airway, while bronchoscopic examination had revealed the trachea to be almost entirely obstructed by a pulsating mass, the obstruction would seem to have been due to dynamic dilatation of the largest aneurysm during life. One can merely speculate as to the cause of the sudden dilatation. The acute episode began while the patient was drinking through a straw, and it is conceivable that he might have aspirated some liquid, initiating asphyxia, and that the resultant rise in blood pressure produced dilatation of the aneurysm with further asphyxia, and thereby a vicious circle. The elevation in blood pressure and absence of tachycardia shortly after the onset of acute respiratory distress are characteristic of the first phase of asphyxia. The slight relief that was afforded by use of the endotracheal tube and administration of oxygen must have been due principally to aspiration of secretions, since the tube did not pass the site of obstruction.

The presence of four aneurysms in association with aortic regurgitation is unusual. The fact that three of the aneurysms were small was perhaps due to the aortic regurgitation, since enlargement of the aneurysms would not tend to occur in the presence of a lowered diastolic pressure.

SUMMARY

Aneurysms of the thoracic aorta commonly press upon the trachea or bronchi with resultant respiratory difficulty. Acute asphyxiation as the cause of death in patients with such aneurysms is rare. The present report describes a patient who died of acute asphyxia when an aortic aneurysm suddenly obstructed the tracheal lumen. This occlusion was observed bronchoscopically, yet at necropsy the tracheal lumen, though narrowed, was not occluded, suggesting that the tracheal obstruction during life was due to dynamic dilatation of the aneurysmal sac. An incidental finding was the presence of three smaller aneurysms of the thoracic aorta of syphilitic origin.

RESUMEN

Los aneurismas de la aorta torácica generalmente causan presión sobre la tráquea o los bronquios con la resultante dificultad respiratoria. Es muy raro que la asfixia aguda sea la causa de muerte en pacientes con tales aneurismas. En este informe se describe un paciente que murió de asfixia aguda cuando un aneurisma aórtico repentinamente obstruyó la luz traqueal. Se observó esta oclusión broncoscópicamente, sin embargo, en la autopsia, aunque la tráquea estaba angostada no estaba obstruida, lo que sugiere que la obstrucción traqueal durante la vida se debió a dilatación dinámica del saco del aneurisma. Un hallazgo concomitante fue la presencia de tres aneurismas más pequeños de la aorta torácica de origen sífilítico.

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Chronic Bilateral Basal Pulmonary Fibrosis*

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Chronic bilateral basal pulmonary fibrosis has been selected to designate a condition characterized by chronic cough, moist rales at the lung bases and basal pulmonary infiltration as revealed by x-ray inspection. In some patients presenting these abnormalities, etiological factors can be determined. In others, present methods of diagnosis and prolonged observation fail to reveal the basic causes.

Cough is not infrequently a symptom for which individuals seek medical attention. It is the concern of the patient and the responsibility of the physician that tuberculosis be discovered or excluded. Established silicosis may also be excluded. Paranasal sinus disease and other upper respiratory etiologies may logically be omitted from consideration.

Chronic basal pulmonary infiltration, as revealed by x-ray, may result from a variety of causes. It is important to consider various possible pathological conditions when basal pulmonary fibrosis is discovered.¹⁻³ In a review of Chronic Nontuberculous Pulmonary Infections in 1939, Hamman⁴ presented evidence which would seem to justify the assumption that many of the chronic basal infections of the lungs are a form of bronchiectasis. Ehrlich and McIntosh⁵ reported three cases of obliterative bronchiolitis in patients dying with uremia, postulating that a disturbance in metabolism in this state may account for the exudation and proliferation. McCordock and Muckenfuss,⁶ in experimental animals, demonstrated that filtrable viruses introduced in proper concentration produced interstitial pneumonitis. This condition favors the subsequent development of fibrosis. In search for the underlying cause one must also consider chronic passive congestion,⁷ fibrosis secondary to emphysema or long standing asthma, cystic disease of the pancreas in children⁸ and radiation pneumonitis.⁹ Similar x-ray shadows are cast by certain stages of lymphogenous dissemination of malignancy,¹⁰ inhalation diseases,¹¹⁻¹² Boeck's sarcoid,¹³ and primary pulmonary arteriosclerosis. More rare conditions such as lipoid reticulo-endotheliosis¹⁴ and leukemic infiltrations occur.

Ninety-nine patients presenting chronic bilateral basal pulmon-

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ary fibrosis have been studied and observed over a period of six months to 10 years. In 18 of these 99 patients, no specific diagnoses have yet been established. Special methods of evaluation have included electrocardiograms, and venous pressure and circulation time studies. Bronchoscopy and bronchograms have been utilized. Vital capacity has been periodically obtained. Sputum examinations, cultures and animal inoculations have been done. Diagnostic therapy has been given for congestive heart failure. Chemotherapy and antibiotics have been employed. Drugs and desensitization to foreign proteins have been used in control of allergy.

The accumulated data revealed that cough, bilateral moist rales and basal fibrosis were associated with specific causes in 81 of 99 patients. Frequently, obscure congestive heart failure was present. Likewise bronchiectasis, pulmonary emphysema or bronchial asthma had been associated frequently with repeated episodes of infection with the production of chronic basal infiltration. Less frequently, lymphogenous dissemination of silent gastric carcinoma presented for a period a pulmonary state of the character under study. Rarely infiltrative primary pulmonary malignancy temporarily presented similar findings. Sarcoidosis in certain instances was confusing. Various pneumoconioses presented predominantly basal abnormalities. In three instances the pulmonary infection and fibrosis associated with cystic disease of the pancreas occurred chiefly in the lower portions of the lungs. In rare instances pulmonary arteriosclerosis was considered as responsible when this judgment was supported at necropsy. Post-radiation fibrosis presented bilateral basal infiltration and moist rales. In this limited group no case of lipoid pneumonia appeared. Fungus disease was not discovered. None of these cases resulted from the long continued use of a tracheal airway. The diminished cough reflex of idiocy, mental deterioration, alcoholism, uremia and unconsciousness was not etiological in this group. Amyloidosis, xanthomatosis and parasitic infestations were not found.

In 18 patients no etiology was discovered. These patients were well nourished, without anemia, diabetes or exogenous nutritional deficiencies. Eleven were females and seven were males. The average age was 56 with a range of 43-73 years. In 11 dyspnea was handicapping. Fever was present, at what appeared to have been the onset, in three. In three others fever occurred in irregular fashion during extended observation. An abnormal eosinophilia of 16 per cent occurred once during a period of fever. Left bundle branch block was present in one electrocardiogram. This patient did not have cardiac insufficiency. In two instances there occurred improvement in the abnormalities revealed by x-ray film. In

general the condition was slowly and irregularly progressive In one instance lung biopsy by needle puncture revealed no useful information

The patients under consideration in this group do not appear to resemble closely the high cholesterol pneumonitis of King and Mallory, the nonspecific pneumonitis of Adams and Kershner, or the chronic pneumonias of Jacobs¹⁵ The following cases are presented to illustrate some of the problems

Case 1 A female, 56 years of age, having chronic cough, wheezing respirations, and exertional dyspnea which had been progressive for one year when first seen in 1940 There was no history of dust inhalation Blood pressure was 170/100, weight 210 pounds Lung areas were resonant but numerous moist rales were heard in both bases Liver was not enlarged There was edema of the ankles Slight clubbing of the fingers was noted Electrocardiogram and routine laboratory tests were within normal limits The original impression was that obesity and hypertension had combined to overload the circulation and that myocardial failure was present The patient did not respond to usual therapeutic efforts In the x-ray film of November 28, 1940 the heart and aortic shadows were about normal in size There was marked hilar enlargement and evidence of extensive infiltration throughout both lungs which was apparently due to fibrosis, most marked at the bases and in the right chest Bronchograms did not reveal bronchiectasis Throughout the observation period extending over eight years, symptoms have persisted with exacerbations and remissions, and frequent episodes of upper respiratory tract infections have been difficult to control Symptomatic relief has resulted from weight loss, ammonium chloride, and bronchial anti-spasmodics An x-ray film of January 25, 1941 showed no clearing, another in February, 1948 revealed persistence of extensive infiltration The patient's weight has been 168-170 pounds Therapy continues to be directed at weight control, symptomatic measures for cough and bronchospasm, and control of recurring respiratory infections with penicillin It is difficult to designate a specific underlying cause of fibrosis in this case

Case 2 This patient, a female, aged 60, who suffered from exertional dyspnea and cough (non-productive), is discussed as one representative of pulmonary congestion secondary to heart failure Her blood pressure was first known to be elevated in 1939 (190/110) Progressive increase in dyspnea occurred Orthopnea developed on several occasions in 1940 Electrocardiogram in 1939 showed T-1 inversion and diphasic T-2 Digitalis was used intermittently from 1940 to 1946 Since 1946 the patient has been continuously on digitalis and mercurial diuretics have been necessary at frequent intervals in the past year to prevent peripheral edema, liver enlargement, and severe dyspnea An x-ray film on April 5, 1946 revealed a considerable degree of hypostatic congestion, more marked on the right Increased linear markings were present in both bases There was tremendous enlargement of the heart X-ray films before and since are no different The patient is reasonably well on a program of limited activity, digitalis, intermittent mercurial diuretics and a low salt diet The infiltrations noted in this case appear to result from chronic passive congestion

Case 3 A male, aged 44, is presented as one illustrating inhalation disease. Onset of cough and shortness of breath began five years ago. He was exposed to irritation from dusts of various kinds over an eight year period. He does research work with metal powders. The cough is most marked in the morning with production of white mucus. Vital capacity is 1900 cc. X-ray film shows rather extensive infiltration in both lungs, mostly at the bases with clear apices. The heart and aorta are normal in size and shape. The sputum and gastric washings are negative for tuberculosis. Venous pressure and circulation times are normal. History and findings suggest pneumoconiosis.

Case 4 A female, aged 40, who is presented as one with acute infection accounting for basal infiltration and is not one of the ninety and nine. She had an acute onset of cough, mucopurulent sputum, chilly sensations, and fever of 101-102 degrees which developed one week prior to admission. This patient attended an ill friend who died of virus type pneumonia two weeks prior to her admission. Sulfonamide therapy was begun five days before admission and was discontinued because of nausea and vomiting. Penicillin was then administered but cough and fever persisted and she was admitted to the hospital. The white blood count on admission was 7,340, polymorphonuclear leukocytes 74, hemoglobin 12.2, cold agglutinins 1:64 on admission and rose to 1:4096, 12 days later. No pneumococci were found in sputum smears. An x-ray film showed the heart and aorta to be normal in size, moderate hilar enlargement with multiple calcified hilar nodes on the left side. Accentuated linear markings were seen in the left base and increased density was present in the lower right lung with obliteration of the costophrenic sinus. A film on October 20, showed almost complete clearing of the consolidation in right lower lung field, but there was still increased density with evidence of pleural reaction. The bronchovascular markings were still somewhat heavy. The findings in this case would indicate atypical pneumonia (virus?). Although permanent bronchiectasis is said to be rare following atypical pneumonia, increased markings, delayed resolution and persistent cough may be sufficient presumptive evidence to warrant bronchoscopy and bronchography.

SUMMARY

It is realized that lesions casting similar shadows by x-ray may be quite different when microscopically examined. Also, comparable tissue changes may result from various causes. With failure of the self-cleansing mechanism of the lung fibroblastic proliferation and replacement can occur whether the substance retained is congestive or infectious in nature, metabolic in origin, or derived from inhaled particles. The cleansing function of ciliary action, bronchial peristalsis and cough is considered to be absent in normal terminal bronchioles. Alveolar cleansing is by lymphatic drainage and phagocytosis. The ultimate lymph channel from the lung is stated by Drinker¹⁶ to be of small caliber with the mechanical effect of a bottle neck. Exudation in excess of absorption can occur with ease.

Pending additional knowledge regarding idiopathic basal pulmonary fibrosis, the therapy attempted has been to arrest further

progress of the disease by the prevention and treatment of recurrent respiratory infections which are frequent, for the symptomatic relief of ineffective cough, and to control alveolar exudation. One consistent feature in the group studied has been age with its increased tissue vulnerability. In a population of increasing age it is probable this condition will be seen more frequently, recognized more easily and ultimately treated more effectively.

RESUMEN

Se reconoce que lesiones que producen sombras semejantes en la radiografía pueden ser muy diferentes cuando se las examina microscópicamente. Además, causas diversas pueden producir alteraciones histológicas comparables. Cuando fracasa la función autopurificadora del pulmón, puede ocurrir proliferación y sustitución fibroblástica, ya sea la sustancia retenida de naturaleza congestiva o infecciosa, de origen metabólico o derivada de partículas aspiradas. Se considera que la función purificadora de la acción ciliar, de la peristalsis bronquial y de la tos, no existe en los bronquiolos terminales normales. La purificación alveolar tiene lugar mediante los vasos linfáticos y la fagocitosis. Drinker¹⁶ afirma que el último canal linfático que emerge del pulmón es de pequeño calibre y causa el mismo efecto mecánico que un cuello de botella. Por lo tanto, es muy fácil que la exudación exceda a la absorción.

Mientras se obtengan conocimientos adicionales sobre la fibrosis pulmonar basal idiopática, se ha empleado una terapia para detener el progreso de la enfermedad mediante la profilaxis y el tratamiento de las infecciones respiratorias que ocurren con frecuencia, para el alivio sintomático de la tos ineficaz y para combatir la exudación alveolar. Un rasgo invariable del grupo estudiado ha sido la edad avanzada con el aumento concomitante en la vulnerabilidad de los tejidos. Es probable que en una población cuya edad esta aumentando se encuentre este estado con más frecuencia, se lo reconozca más fácilmente y al fin se lo trate más eficazmente.

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D I S C U S S I O N

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Since the use of x-ray has become universal we are not satisfied by interpreting rales in the base of the lung as simple bronchitis. Chest specialists have been baffled by the many varieties of diffuse pulmonary infiltrations, especially in the lower areas of the lungs. There is, however, no other group of pulmonary diseases which shows up the inadequacy of x-ray diagnosis quite as much. While x-ray is unexcelled in demonstrating the presence of pathology, it is by no means unexcelled in differential diagnosis.

We should be careful in the use of the word fibrosis. Within the range of the x-ray appearance of these conditions are also malignancies, especially the diffuse perilymphatic and peribronchial infiltrating carcinomas. Some of us may be a little more experienced than others in differentiating basal infiltrations by x-ray, but essentially the roentgen diagnosis always remains guesswork and diagnosis must be made by other means. As the authors pointed out, some of these conditions—in their report 18 per cent—defy all attempts at diagnosis, occasionally even on macroscopic inspection at autopsy.

How insecure our clinical criteria are was demonstrated to us by the case of a woman, who had this type of diffuse infiltration. She was suspected of having sarcoidosis, because of the experience with the elevation of gamma-globulin values in the blood serum.

in that disease Her gamma-globulin value was the highest we had ever obtained in any patient She died, and the pathologists were certain that she had not had sarcoidosis The final pathologic diagnosis was scleroderma of the lung

Dr Volini, in the closing remarks of his paper, mentioned the work of Arnold Rich, who has called attention to the anaphylactic reactions following chemotherapy He has pointed to periarteritis nodosum in patients as the result of treatment by a variety of agents, especially by the sulfonamides, and has proved his point by animal experiments He has also pointed out that many of these pulmonary infiltrations can be the result of such anaphylactic reactions

I wish to congratulate the author on this presentation We should have more papers dealing with these baffling conditions, which are slowly progressive but almost invariably lead to death by secondary cardiac involvement The possibility of tuberculosis in these diffuse infiltrations should not be lightly discarded The diffuse, chronic, slowly progressive type of tuberculous disease, often termed senile tuberculosis, should be considered a diagnostic possibility even if the tuberculin test is negative, tubercle bacilli in the sputum may be found either not at all or in very small numbers and only occasionally

A CARLTON ERNESTENE, M D
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The etiologic factor in chronic bilateral basal pulmonary infiltration usually can be discovered without too great difficulty There is, however, a sizeable group in which accurate diagnosis cannot be made even after the most detailed investigation Careful and complete studies are indicated in every case that presents the type of x-ray picture Dr Goodrich has reported This is necessary not only to guide one in recommending the appropriate type of medical treatment, but also to detect those cases which, with the steady progress of thoracic surgery, may be amenable to surgical management In this latter respect, instances of unilateral basal pulmonary fibrosis often present a more important diagnostic problem, for it is in this group that the number of cases in which thoracic surgery will be indicated is greater In individuals who have unilateral pulmonary basal fibrosis, particular emphasis should continue to be placed upon the need for early bronchoscopic examination Time spent in merely observing the clinical or roentgenographic progress in patients who have unilateral processes may mean the loss of that margin which is so necessary for successful surgical intervention

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Dr Goodrich is to be congratulated for bringing to our attention the chronic bilateral basal lesion, about which too little thought is given. It would seem that this sort of lesion is the penalty we pay for being animals that walk in the upright position. It is due to lack of drainage in the basal areas of the lung. In a clinic in which a large number of patients with pulmonary complaints are seen, we are more and more aware that these so-called minor bronchial conditions which do not annoy the patient particularly but continue for a long time, eventually become serious. Some years ago the medical profession did not have to worry about that, the patient died of cancer or tuberculosis or some other infection long before these conditions caused any complaint.

These minor chronic conditions are becoming major problems. It would seem that not all of them by any means can be classified as fibrosis. The majority are dependent upon residual infection in the bronchi and lack of drainage, or an area of atelectasis. Those conditions will produce fibrosis, but I believe emphasis must be laid on the fact that atelectasis without infection will not produce fibrosis. We have all known lungs to expand after a period of years, without evidence of fibrosis. We come back to the question of infection, and our observations on patients with chronic conditions in the chest have indicated that there is infection in every case, and we can isolate the organisms present in the infection, regardless of whether or not the patient is suffering from the infectious condition. These minor conditions must be treated as potentially serious ones. Once they become well established therapy is increasingly difficult. While they are minor and causing no symptoms they should be checked before irreversible changes occur.

Dr Goodrich mentioned temporary bronchiectasis. I do not believe in that. Temporary dilation of the bronchi, perhaps—but bronchiectasis represents permanent expansion, and I do not believe the bronchi can be returned to a normal state. Dr Ernestene mentioned unilateral fibrosis and the possibility of surgery. But careful study of a lung that shows no shadow often reveals it to be as diseased as the one that does. We may see it change from one side to the other, year after year it may be evident on one side, then change to the other. It is due to lack of drainage to obstruction. The use of aerosol therapy, and most of all, adequate positional drainage or bronchoscopic drainage if necessary, may prevent these conditions. I think as time goes on we will have more and more patients of the type we have discussed today.

Closing Remarks

Ben E Goodrich, M D , F C C P I could hope for nothing better than to attend some meeting in the future when one of these discussants and any others will more ably consider this subject and present reports thereon

Dr Bloch comments on the use of the term fibrosis when it is likely the infiltration at times is not fibrosis The use of this term is inherited from x-ray in that a chronic persisting basal pulmonary infiltration is not infrequently designated as fibrosis by the radiologist Fibrosis has been reported to result from various diseases of diverse origins Allergic responses may produce tissue fibrosis whether chemotherapeutic in origin or on an experimental basis as shown by Rich Possibly some portion of the tissue change in primary atypical pneumonia may be of this origin

Dr Bloch stresses the diffuse basal lesions of pulmonary tuberculosis particularly in the elderly patients Those patients who proved to have tuberculosis, were excluded from this report It is possible that among the undiagnosed group, tuberculosis as yet undiscovered, may be present and he has inferred that surety cannot be established short of microscopic examination

Dr Ernstene states that one cannot overstress the importance of malignancy, especially in patients where the lesions are more localized This is, as he says, important because there is the possibility of surgical removal

Dr Levine mentioned the importance of infection Whatever the original cause, once established, repeated infections become a great part of the problem and the necessity is great for prompt treatment of episodes of even minor infections in the elderly

The word temporary bronchiectasis was inferred because of dislike for the word pseudo-bronchiectasis as used by Blades to designate the temporary dilatation of bronchi following atypical pneumonia Dr Blades' point is well taken that bronchiectasis following primary atypical pneumonia should not be surgically treated since the bronchial dilatation may be of temporary nature

Basal Tuberculosis Simulating Sub-Phrenic Abscess*

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Because of its insidious nature a subdiaphragmatic abscess may not manifest itself until it has progressed to the stage of causing pulmonary pathology. Pleuro-pulmonary involvement such as effusion, pneumonitis, atelectasis, etc., at the base of the lung on the involved side may be the first changes to call to mind the possibility of sub-phrenic pathology. The following case is of interest because the history, physical findings, and roentgenograms were consistent with the diagnosis of subdiaphragmatic abscess, but subsequently the pathology was proved to be due to tuberculosis localized in the basal segments of the right lower lobe.

J P, R No 3279, is a 60-year old white male who has been hospitalized for the past 20 years because of paranoid schizophrenia. Previous to his present illness, he had always been in good health, and numerous physical examinations and chest roentgenograms had been entirely negative. On December 5, 1946 a chest roentgenogram was reported as negative and a review of this film showed no evidence of infiltration or scarring due to an old arrested lesion. On February 4, 1947 he complained of abdominal pain, was distended and appeared pale. Roentgen studies revealed evidence of intestinal obstruction. Laparotomy was performed the following day when a volvulus of the sigmoid was relieved and a colostomy performed.

The postoperative course was unsatisfactory due to a low grade fever with frequent high spikes accompanied by leucocytosis. There was no cough and the patient would not comment on his complaints. A roentgenogram of the chest on February 14, 1947 revealed increased markings of both lung fields probably due to elevation of the diaphragm (Fig 1). There was a small amount of air under the right leaf of the diaphragm remaining from the previous operation. This demonstrated a smooth diaphragmatic contour. No evidence of infiltration in the lung was observed.

The patient remained chronically ill and penicillin therapy was administered for approximately two months. A film of the chest on April

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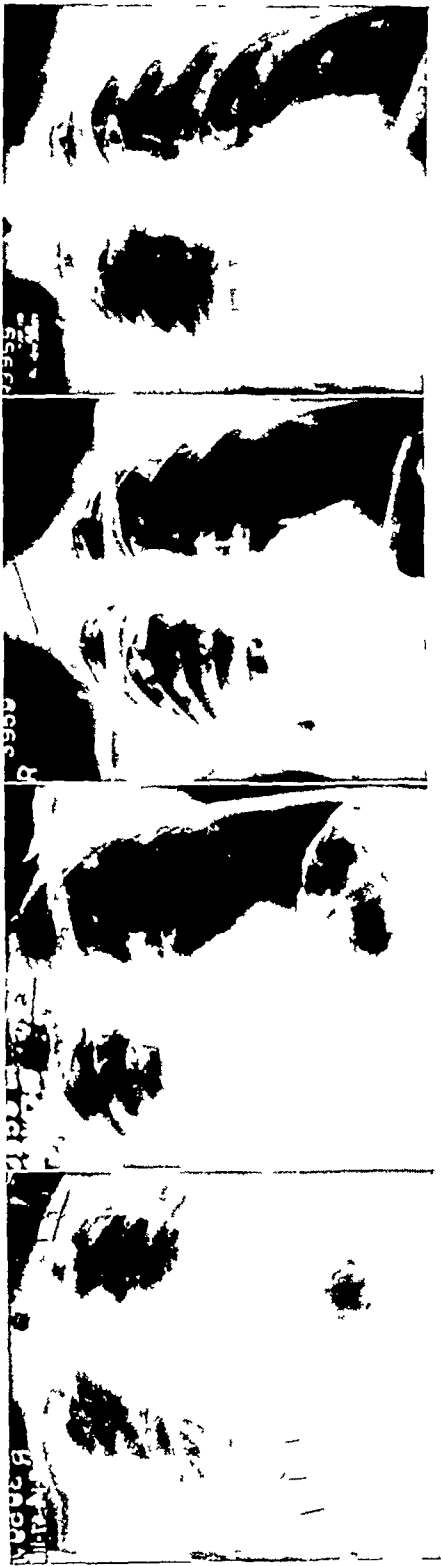


FIGURE 1 Roentgenogram of the chest showing air under the right leaf of the diaphragm and demonstrating smooth diaphragmatic contour (2-14-47) —Figure 2 Pleuro-diaphragmatic effusion obscuring underlying parenchymal detail (4-21-47) —Figure 3 Multi-locular fluid levels at the right base with irregular parenchymal infiltration — Figure 4 Dense pleural thickening at the right base, obscuring parenchymal detail

21, 1947 revealed a dense pleuro-diaphragmatic effusion extending up to the middle of the chest wall on the right side, obscuring underlying parenchymal detail (Fig 2) The remainder of the lung fields showed no evidence of abnormality The possibility of subdiaphragmatic pathology was suggested

The colostomy was closed on May 13, 1947 On May 29 an abdominal fistula was noted to be draining fecal material Lipiodol was instilled into the fistulous tract and a communication with the sigmoid colon was demonstrated roentgenographically In July, 1947 it was noted that the patient had a cough and raised yellow, foul-smelling sputum Studies at that time revealed no evidence of tubercle bacilli on smear or culture The patient failed to gain weight and appeared chronically ill, although he was now ambulatory

Serial roentgenograms of the chest over the next three months revealed evidence of multi-locular fluid levels at the right base with irregular parenchymal infiltrations in the underlying lung field The remainder of the lung fields still remained clear (Fig 3) The persistence of the pleuro-pulmonary changes at the right base had prompted the X-ray Department on numerous occasions to suggest the presence of sub-phrenic abscess On October 1, an exploratory operation was performed The subdiaphragmatic space on the right was approached posteriorly by removal of the 12th rib The peritoneum was incised and the right anterior and posterior subhepatic spaces were palpated Finger dissection was carried superiorly over the lateral right ligament of the liver to the bottom of the diaphragm but no area of suppuration was found

The postoperative course was uneventful, but the patient remained unimproved By December 12, 1947 the abdominal fistula had closed On January 28, 1948 a pleural tap was done, and a smear of the fluid showed tubercle bacilli This diagnosis was verified by gastric cultures Pneumoperitoneum was attempted, but was not successful because of massive adhesions The patient has done moderately well on bed rest and at the present time he has dense pleural thickening at the right base obscuring parenchymal detail (Fig 4)

Discussion

Thoracic complications are common in cases of sub-phrenic abscess, Claggett,¹ for example, found them in 65 per cent of his cases While the clinical findings in this case suggested subdiaphragmatic abscess, the roentgenographic finding of a basal pleuro-diaphragmatic fluid accumulation was compatible with various other infra and supra-diaphragmatic lesions These include diaphragmatic hernia, ovarian tumor (Meigs Syndrome), hepatic abscess, inflammation or tumor, inflammatory changes of the lung and pleura, pulmonary neoplasms, heart disease, and eventration of the diaphragm Basal pleural fluid² for example, has been described as causing apparent elevation of the diaphragm

As pointed out by Reisner³ it is important to distinguish between tuberculous infiltrations of subapical portions of the lower lobes and those involving the basal segments since the latter is

much more uncommon Tuberculosis should not be forgotten when a puzzling lower lobe lesion is being investigated and repeated laboratory studies should be performed to rule it out

Reisner³ has postulated that a high diaphragm or one with restricted movement may cause poor aeration of the lower lobe and that this is a predisposing factor to lower lobe tuberculosis. This may apply in the above case since splinted respiration with limitation of the diaphragmatic excursion is expected following abdominal operations

SUMMARY

A case of basal tuberculosis simulating subdiaphragmatic abscess is reported and discussed

RESUMEN

Se presenta y discute un caso de tuberculosis basal que parecía ser un absceso subdiafragmático

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Surgical Therapy of Pulmonary Tuberculosis at a Veterans Administration Chest Center*

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Indications and variations in the surgical approach to pulmonary tuberculosis are still in a state of constant change and while a few procedures have become permanent fixtures in the thoracic surgeons armamentarium, there are numerous satellite operations popular with some and rejected by others, all this bearing testimony to the fact that in the absence of a definitive chemotherapy or antibiotic agent able to eradicate the disease there remains many a therapeutic problem allowing more than one answer. Frequently, therefore, in the field of surgery of tuberculosis the question of what to do and when to do it is settled by a cooperative effort through a conference in which medical men, roentgenologist, pathologist and surgeons participate. The make up of a large medical organization functioning on a nationwide scale as the Veterans Administration does, requires and promotes the cooperative effort of medical men of different training and background, representing various schools of thought.

The exchange of ideas on various aspects of the management of the surgical problems dealt with, quickly culminated in the development of a common approach and a therapeutic policy combining elements stemming from different trends of thought and representing a digest of experience gained not only at this institution but at various other hospitals as well, with which the individual surgeons of the group happen to be affiliated.

Additional points of interest have come up in connection with the use of streptomycin in the surgery of tuberculosis. The main problems having arisen in this respect are (1) Evaluation of the efficacy of the antibiotic agent to prevent and to combat spreads (2) The high incidence of streptomycin resistance and the necessity therefore of proper timing of antibiotic treatment and surgery.

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Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for opinions expressed or conclusions drawn by the authors. The authors wish to acknowledge the guidance given in the therapy of the cases included in this paper by the Consultants in Thoracic Surgery, Dr Daniel A Mulvihill and Dr Charles W Lester

(3) Advances made in the surgery of pulmonary tuberculosis since the introduction of streptomycin and changes in the indications of the various technical procedures in connection with the use of the drug

While the patient material of this hospital (Castle Point) is obviously not large enough to permit final conclusions and answers to these problems, enough experience has, however, been gained to indicate some definite trends

The hospital cares for an average census of about 600 patients with a fairly rapid turnover. Activities of the surgical service include bronchoscopic, bronchographic, and respiratory functional work-up in addition to the various operative procedures. The period from March 1947 to March 1948 has been arbitrarily selected for review. The overall activities of the service for this period of time are given in Table 1 (compiled November, 1948)

TABLE 1

1) MAJOR PROCEDURES		
a) Thoracoplastic operations		108
(1) 1st stages	40	
(2) 2nd stages	37	
(3) 3rd stages	28	
(4) 4th stages	3	
b) Revisions		9
c) Open pneumonolysis		5
d) Resection for pulmonary tuberculosis		12
e) Thoracotomies		5
f) Pleurectomies		2
g) Cavernostomies		2
h) Closure of cavernostomy by muscle flap		2
		<hr/> 145
2) MINOR PROCEDURES		
a) Scapulectomies		4
b) Phreniclasia		55
c) Closed pneumonolysis		53
d) Bronchoscopy		123
e) Bronchography		21
f) Bronchspirometry		11
		<hr/> 267

A total of 145 major procedures has been carried out for the treatment of pulmonary tuberculosis. There has been no mortality. Table 2 gives a survey of complications encountered in this group.

TABLE 2

1) Tuberculous spreads	5
2) Wound infection, tuberculous	1
3) Wound infection, pyogenic (abscess)	1
4) Cardiac decompensation	1
5) Wound disruption	1

Each of the complications will be discussed further in connection with the type of procedure following which it occurred

Closed and Open Intrapleural Pneumonolysis

The severance by surgical means of adhesions occurring during pneumothorax treatment is an ancillary procedure, the end results of which are dependent upon the efficacy of the pneumothorax proper. No effort will therefore be made to evaluate results in terms of sputum conversion. Emphasis should be placed upon complications encountered in the performance of pneumonolysis and upon results in terms of technical perfection of the pneumothorax in a given case. As far as the indications are concerned it has become our guiding rule that a pneumothorax which is unsatisfactory due to the presence of adhesions had best be abandoned and be replaced by some other form of therapy inasmuch as complications are prone to follow sooner or later. If one feels that it is desirable to maintain a pneumothorax the feasibility of severing existing adhesions can only be ascertained by exploratory thoracoscopy. (The optimum time for thoracoscopic exploration is between six and eight weeks after induction of pneumothorax.)

It has become our practice to attack only the simple band and string adhesions by direct division of the adhesion proper near its parietal attachment. All other types of more extensive adhesions have been removed by enucleation in the extrapleural plane. The crux of the situation lies, of course, in the decision as to how extensive a procedure may be permissible. The yard stick in this respect has been the distribution of disease. In unilateral cases wide dissections have not been attempted. Unilateral cases in whom it appeared to the operator that lysis could not be completed in one session and without denuding large pleural surfaces have been rejected and recommended for some other type of surgery. The frequent occurrence of postoperative sero-hemorrhagic effusions even though these might be benign and not necessarily lead to tuberculous exudates, carries with it a high percentage of poor results as far as pulmonary function after future re-expansion is concerned. In addition there is the even greater risk of specific and mixed infection in the pleural space, a risk which is not acceptable in cases with unilateral disease.

In the presence of bilateral disease with cavitation in both lungs where control of one side by pneumothorax would appear to be mandatory the indications for lysis have been somewhat wider. However even in this type of case we have been reluctant to perform important decollations especially where the adhesions involved the mediastinal surface. In the literature there exists a

wide divergence of opinion in regard to this type of lysis. While one group of operators testify to the innocuousness of the procedure and back this opinion up with statistical data others are set against wide decollations and point to the high incidence of pleural complications. Obviously, in this type of tedious and often technically difficult procedure the individual skill becomes an important factor. A few facts deserve to be stressed no matter how skillful the operator, when wide decollations are undertaken. First, the field of vision is often partially limited and as soon as some bleeding has occurred tissues can no longer be identified with absolute certainty. Second, the degree of penetration of the heat liberated by the cautery cannot be gauged with accuracy. These two factors create a situation beyond the control of the operator. Reasoning along these lines one is led to the possibilities of open lysis by thoracotomy and the indications thereof. Surgical invasion of the pleural cavity for the purpose of lysis of adhesions is an old procedure. The experience in earlier years or rather in earlier decades has by and large been unfortunate and marked by a high incidence of pleural infections. It was only natural that with the advent of newer techniques and of the antibiotics attention was again given to the procedure. There is no doubt that invasion of the pleural cavity has become much safer now. One cannot help feeling that the trauma inflicted upon the pleural surface by open thoracotomy is hardly greater than when the procedure is done by the closed method. We believe it is smaller and what is even more important, the dissection can be carried out with greater safety under direct vision in the extrapleural layer if necessary and whatever bleeding may occur can be adequately controlled. Inspection of the pleural cavity during the preliminary thoracoscopy will give important information on the state of the pleural surfaces and will eliminate those cases in which the presence of visible tuberculous involvement presages complications. The pleural sequelae should be identical in both types of procedures. Some deposit of fibrin on the pleural surfaces must evidently be expected and will undoubtedly lead to some functional impairment after future re-expansion. The risk in this respect would seem no different in the open than in the closed procedure. We have felt justified in recommending open pneumonolysis in a small number of cases with bilateral disease rather than to accept the risk of wide decollations by closed pneumonolysis. Table 4 shows the proportion of each indication in the total number of cases.

- The posterolateral or the anterior approach have been used with or without removal of a rib. The chest was closed tightly. Streptomycin was given systemically for one week preoperatively and

TABLE 4

1) Closed intrapleural pneumonolyses		53
a) Remained exploratory thoracoscopies	14	
b) Lysis performed	39	
c) Complications in this group		
(1) Tuberculous empyema		0
(2) Mixed infection empyema		1
(3) Benign temporary effusion		8
(4) Subcutaneous emphysema, marked		15
(5) Adhesive pleuritis		0
2) Surgical intervention for the establishment of a pneumothorax space		5
a) Complications in this group		
(1) Tuberculous empyema		0
(2) Benign temporary effusion		5
(3) Mixed empyema		0
(4) Adhesive pleuritis		0

for two weeks after the procedure and one gram of the drug was left in the pleural cavity at the time of operation but none was instilled intrapleurally during the postoperative course. Constant attention must be given postoperatively if the space is to be maintained successfully. As many as four aspirations and refills have been necessary during the first 24 hours after operation. Sero-sanguinous exudate in the pleural cavity should be removed completely and with great care so as to avoid deposits on the pleural surfaces and obliteration of the space by adhesive pleuritis. Though the number of cases is small we have been satisfied with the result in four of five cases. Two of the cases present new and interesting features and will be discussed in greater detail, as they demonstrate an extension of the procedure into a new field from the technical point of view. Both cases presented bilateral lesions. In the first case a pneumothorax space had been present on one side but had subsequently been lost while the patient had left hospital care temporarily against medical advice. The second case never had a pneumothorax and attempts to create one had failed on both sides. In both cases a pneumothorax space was established surgically with success by the open method and their postoperative course was entirely uneventful and in no way different from the remainder of the group. While the procedure was technically successful in the first case the clinical result was disappointing for the cavity present did not close and its behavior suggested the presence of a tension mechanism. While this, of course, was suspected preoperatively, no definite prediction could have been made as to the behavior of the cavity under pneumothorax and as control of one side was imperative and no other method available it was decided to perform the procedure. Since then the pneumothorax has been re-expanded and no ill results have followed. We feel

that this occurrence is important as it has bearing on the choice of cases for the procedure

To summarize the indications briefly Open pneumonolysis has been recommended in bilateral cases in whom control of one side appeared to be mandatory The open method has been chosen in preference to wide decollation by the closed procedure In two cases a pneumothorax space has been artificially created by surgical means This has been technically successful in both cases undertaken While the procedure was entirely satisfactory from the clinical point of view in one case, in the second instance the lesion was resistant to the pneumothorax, due to the type of lesion encountered Of a group of 53 cases with adhesions complicating an otherwise desirable pneumothorax 39 were sectioned by the closed method, three were sectioned by the open method and 11 remained exploratory and re-expansion was recommended

Thoracoplasty

During the one year period covered by this report a total of 108 thoracoplastic operations were performed These include 40 first stages, 37 second stages, 28 third stages and 4 fourth stages While the majority of these procedures were performed for the treatment of parenchymal lesions some were carried out for obliteration of an empyema space, resulting from either mixed or pure tuberculous pleural infections In this latter group, are a few cases with controlled underlying lungs The indications in this group conform to the classical concepts In the technique there has been one variation that deserves further discussion The cases fall roughly into two categories In approximately half of the cases the transverse process of the first rib was left in In the second group the transverse process of the first rib was removed There is no additional technical difficulty in this procedure and the resulting anatomical collapse compares favorably with that obtained in the first group The x-ray shows that regeneration of the bony plate sets in closer to the spine and the gutter usually seen between spine and bony plate fails to develop The upper portion of the lung seems anatomically better collapsed It is fully realized that perfect anatomical collapse does not necessarily entail a good clinical result which to a great degree depends upon the type of pathology being collapsed by the procedure There has been no significant difference obtained in the clinical results and the number of conversions has been about the same in both groups However, it should be borne in mind that the total number of cases is so small that differences in the pathological type of lesion treated will decidedly have a greater influence on the results than a slight variation in technique While a good technical and

anatomical result by no means insure healing of the lesion it is to be emphasized that the aim should still be anatomical collapse as nearly perfect as possible. The results obtained in this group are in line with those reported from other institutions. The following figures are for those cases in whom at least four months of follow-up are available and in whom the thoracoplasty has been performed for the control of a parenchymal lesion

Total number of cases	23
Apparently arrested with sputum negative on concentration for more than 6 months and cultures, cultures negative on activity	11
Quiescent, with sputum negative for more than 6 months	5
Improved with predominantly negative sputum but occasional positive sputum	2
Thoracoplasty failures with positive sputum	5

Far more interesting is the occurrence of complications. Streptomycin has been employed pre and postoperatively in alternate cases. This has been done according to the protocol of a nationwide study conducted by the Veterans Administration (This protocol has recently been discontinued and future surgical cases will be treated with streptomycin only when this appears to be specifically indicated). Alternate cases of a consecutive series have been given streptomycin for one week preoperatively and for two weeks postoperatively. In the treated group eight cases in whom 21 operations were carried out have received a daily dose of two grams and three cases with nine operations have received a daily dose of one gram. No serious renal or allergic complications of the drug have been encountered. Almost all of the two gram cases developed vertigo whereas none of the one gram group showed this condition. The complications following thoracoplasty with and without streptomycin were as follows

- 1) Wound disruption occurred in one non-streptomycin treated case. Wound healed secondarily.
- 2) One late wound abscess (pyogenic) occurred in a non-streptomycin treated patient and healed uneventfully after revision and drainage.
- 3) One case developed cardiac failure after the second stage and the thoracoplasty was not carried any further.
- 4) Spreads

In the streptomycin group	1
In the control group	3

Only the tuberculous spreads are of significance in relation to the streptomycin treatment. In this particular group there was a definitely higher incidence of postoperative spreads in the non-treated group. It is only fair to state that we understand that in the overall picture gathered from the entire Veterans Adminis-

tration setup this discrepancy has failed to develop. It might well be that in such a small series as ours differences in pathology tend to have greater weight in the picture than they would have in a larger series. All spreads in the non-streptomycin group, once recognized as such, have after a suitable period of observation, received streptomycin and have cleared up satisfactorily. None has interfered with the completion of the thoracoplasty and none has needed additional treatment with the antibiotic. Table 5 gives a picture of the total number of operative cases (thoracoplastic and other procedures) having received streptomycin. It shows that only two spreads occurred in the entire group of 35 patients having undergone 63 operations.

<i>Procedure</i>	<i>Cases</i>	<i>Streptomycin q24h</i>	<i>Operations</i>
Thoracoplasty	8	2 gm	21
Thoracoplasty	3	1 gm	9
Lobectomy	4	2 gm	4
Lobectomy	3	1 gm	3
Pneumonectomy	4	1 gm	4
Revisions	3	2 gm	3
Revisions	3	1 gm	3
Thoracoplasty for empyema	2	1 gm)
	1	2 gm) 10
Open pneumonolysis	2	2 gm	2
	1	1 gm	1
Schede	1	1 gm	1
TOTAL	35		63

There is no doubt that streptomycin has a considerable therapeutic effect on the early exudative type of lesion which, of course, is the prototype of pathology present in a tuberculous spread following an operative procedure. It does not influence to any great extent the older type of lesion and cannot by itself bring about closure of areas destroyed by the disease. For these reasons it is obvious that in the treatment of pulmonary lesions the greatest value of the drug is in conjunction with surgical procedures designed either for collapse or removal of diseased areas. The frequent occurrence of resistance to the agent raises an important problem. Approximately 60 per cent of the treated cases seem to develop resistance to the drug. The dose administered has less influence upon this mechanism than the time element. Sixty days seems to be the length of time after which resistance must be expected, regardless of whether a small or a large dosage has been employed.

If this is so, and as there is no possibility of predicting in a

given individual case whether resistance will become manifest, one is under obligation to plan carefully for the use of the drug in conjunction with other therapeutic measures. Frequently, in recent months, as the number of streptomycin treated cases have increased, patients have been brought up for consideration of various surgical procedures to consolidate gains that have been made with the antibiotic. Often surgery has been pushed in order to coincide with the period of effectiveness of the drug. While it is true that probably in many a case this has resulted in the patient's coming to surgery better prepared and at an earlier period than possibly could have been expected before the advent of streptomycin, attention should nevertheless be drawn to the fact that in some cases it would have been better to keep the antibiotic in reserve for a later stage of therapy. It must be recognized that the drug produces resistance in a high proportion of cases and that one must have a long range plan for its use when the need for it is greatest.

One of the problems in the treatment of pulmonary lesions by thoracoplasty is the management of the larger apical cavities, the so-called giant cavity. The results in this particular group of cases have been notoriously poor and a number of procedures have been designed to cope with this difficulty. One of the approaches to this problem has been to combine the collapse procedure with drainage. The most popular method has been an anterior thoracoplasty followed by Monaldi suction through the site, and later completion of the thoracoplasty by a posterior approach. This permits, in cases where the cavity is favorably located, drainage through the anterior site and a posterior procedure which avoids the contaminated field.

In our thoracoplasty series there have been a number of giant cavities, some of them with marked sputum production. A somewhat different approach has been used with satisfaction. Thoracoplasty performed in reverse order, i.e. from below upward, we believe close a higher proportion of these giant cavities when the orthodox thoracoplasty is performed. Original method of doing the lower stages first was used to obviate danger of ipso-lateral spreads into the lower lobe.

The underlying thought was to avoid this occurrence by collapsing the lower portion of the lung first. However, in this procedure probably produces a more gradual collapse of the involved area due to the fact that the infiltrated and thickened chest wall following the lower stages only gradually conforms to the maximum collapse (over a period of perhaps five to ten days) following the last upper stage. After a certain number of cases had been done in this particular way it became apparent that

astonishingly good collapse could be obtained by this method and that a high percentage of the so-called giant cavities will yield to this approach

Excisional Surgery

Differences of opinion still exist with regard to the indications and the results of excisional surgery in the treatment of pulmonary tuberculosis. Since the improvements in operative technique and anesthesia have made the removal of tuberculous pulmonary tissue a practical procedure, the pendulum of opinion has made a wide swing. During the earlier phase of the experience with the procedure, the emphasis has been on a reduction in the immediate postoperative mortality, avoidance of complications, and generally speaking on a widening of the indications in order to test the limits of the procedure. Today the picture has changed. There is little postoperative mortality in most hands and the emphasis now is given to an investigation of the long range results and upon the proper selection of cases from that point of view. As the follow-up periods have increased the indications have been reduced to narrower limits.

During the one year period selected for this study twelve resections have been performed. The relative frequency with which recommendation for resection has been recommended in comparison to other procedures is as follows: during the same period of time 108 thoracoplastic procedures have been done (in approximately 40 cases) and another 25 cases have been recommended for various other procedures like revisions, etc.

No mortality has occurred in this group of resections. All cases have been treated with streptomycin for one week preoperatively. Postoperatively these cases have received streptomycin for 60 days. The only complication that has occurred in this group has been one contralateral spread in a pneumonectomy case. There has been some resolution of this bronchogenic seeding with the streptomycin but the clearing has not yet been complete.

It has been routine policy to follow the resection with limited thoracoplastic procedures to avoid over-distension of the remaining parenchyma.

There is nothing in the technique we have employed that deserves special mention. Particular attention has been paid to obtaining a bronchial stump as short as possible and to closure of the stump by simple, longitudinally placed, terminal sutures. There is no need to emphasize the all important part played by the anesthesia team in maintaining adequate oxygenation and keeping a clear tracheo-bronchial tree at all times. These are

fundamental for good results in this type of surgery The indications in these 12 cases are given in the table below

Total number of excisions	12
Lobectomies	6
Segmental resections	1
Pneumonectomies	5
Indications	
A) Lobectomy	
1) Tuberculoma (isolated, solid or semi-solid Caseocoe focus)	2
2) Upper lobe lesion with broncho-stenosis	2
3) Thoracoplasty failure	1
4) Lower lobe cavity (resistant to pnx)	1
B) Segmental	
1) Tuberculoma	1
C) Pneumonectomy	
1) Thoracoplasty failure	2
2) Combined pleurectomy and pneumonectomy	2
3) Upper lobe lesion associated with lower lobe cavity resistant to pnx	1

General agreement has been reached as to the legitimate indication of resection for isolated tuberculoma, thoracoplasty failure and uncollapsible lower lobe cavity Also, when severe broncho-stenosis is present and a thoracoplasty is therefore contra-indicated, resection becomes the procedure of choice The difference of opinion at present centers upon the group of so-called predicted thoracoplasty failures, i.e. the group of cases of destroyed lungs where there is a great amount of disease but absence of marked bronchostenosis Some feel that the thoracoplasty in this type of case can be predicted to result in failure to close the lesion and that therefore it is better to carry out primary excision Arguments advanced in favor of this approach are that resection after thoracoplasty is technically more difficult and carries a higher operative mortality and that once the chest is open one is frequently confronted with a great deal of disease in the lower lobe and total pneumonectomy must be performed rather than removal of a lobe It is reasoned that the lower lobe disease represents an upso-lateral spread from a lesion incompletely collapsed by the preceding thoracoplasty

While it is impossible with the present length of follow-up available to decide upon the validity of the conception set forth above, attention should nevertheless be brought to several important facts It must be emphasized that it has been a common experience by all those performing thoracoplasties in great numbers that accurate prediction as to cavity closure cannot be made with sufficient accuracy Often collapse done for a relatively small lesion that would appear thin walled, fails and a procedure

carried out for giant cavities or destroyed lungs yields a complete closure and conversion against all expectations. It must also be recognized that even though a thoracoplasty might not close a cavity completely, it still might lead to considerable improvement in a patient's condition. The lesion has been collapsed to some extent, the sputum has diminished, toxicity has subsided and although the conversion is not complete one is dealing with a patient who is in altogether better shape and shows more resistance to the disease. Perusal of the follow-up studies that have appeared in the literature so far would lend support to this view and indicate that while the immediate mortality in the group of resections performed for thoracoplasty failures might be somewhat higher this is still out-weighted by the far better, long range performance of this group.

It seems questionable also whether the extensive lesions found in the lower lobes of those patients who come to resection after thoracoplasty, really represent ipso-lateral post thoracoplasty spreads. It might well be that these lesions were present before the thoracoplasty for it has become common experience, since the advent of resection in larger numbers of cases, that the operator is frequently confronted with an impressing number of foci that he can palpate at the operating table but which he was totally unable to see on the x-ray.

For all these reasons we have felt inclined to recommend that a thoracoplasty be done first in this type of case, to be followed later by resection if conversion is not obtained.

In the above shown table of indications the group of combined pleurectomy and pneumonectomy deserves further discussion. Only a few of these procedures have been done for the treatment of cases complicated by the presence of empyema. The first case of this type carried out at this institution had a previous two stage thoracoplasty done several years ago for the presence of a large apical cavity. This had failed to collapse the cavity to any extent and after the second stage a mixed infection empyema had resulted and had to be drained by a closed thoracotomy. The contra-lateral lung had remained free of disease. While further continuation of the thoracoplasty followed by a Schede operation possibly could have resulted in a good result as far as the empyema was concerned it obviously would have failed to control the parenchymal lesion which had remained widely patent under the upper stages of the thoracoplasty. The problem was a double one, parenchymal and pleural. We felt that the indication to perform a complete excision was perfectly legitimate because one was dealing with a thoracoplasty failure as far as the parenchymal disease was concerned. If the procedure was to be successful it

meant control of the pulmonary lesion and avoidance of numerous thoracoplasty procedures followed by mutilating pleurectomy for the treatment of the mixed infection empyema. Had we been unsuccessful, infection of the pleural space would have resulted, but this was already present. Several of these procedures have since then been performed with uneventful recovery and primary closure of the wound. These cases demonstrate that with the help of streptomycin, an infected pleural space need not stand in the way of pulmonary resection if the latter is indicated. It seems important to discuss the indications of this new technical extension of resection. The crux of the situation lies in a correct evaluation of the parenchymal pathology present, i.e. whether one is dealing with controlled or uncontrolled disease in the underlying lung. Some have felt that it is legitimate to apply combined pleurectomy and pneumonectomy to cases who have mixed infection empyema with controlled underlying disease in order to avoid the mutilating Schede. Again, others have extended the indication to simple tuberculous empyemata with uncontrolled or even controlled parenchymal disease. Although no large experience with these combined resections have been accumulated as yet, one would be inclined to surmise that the morbidity and mortality in this group will prove to be somewhat higher than in the type of case previously done. It is questionable whether it is legitimate to accept this risk in cases with controlled lung disease in order to avoid the sequence of thoracoplasty and Schede. It seems to us that the procedure is definitely not indicated in the group of simple tuberculous empyemata with controlled lung disease in whom one can close the space in a high proportion of cases by simple thoracoplasty with frequent taps between and after every stage. In cases of simple tuberculous empyemata and the presence of uncontrolled parenchymal disease, the type of pathology of the lesion should govern the indication. If a lesion is such that it falls into the group where resection is generally accepted the presence of the empyema need not stand in the way. The same reasoning should apply to the mixed infection empyema case with controlled pulmonary disease. If the parenchymal lesion is of the type that should be resected, resection is feasible and legitimate in the presence of a mixed infection empyema. The latter as has been shown, need not be an obstacle. In cases where the underlying lung is controlled or where the pathology seems to be of a type that does not fit the general indications for resection, we have followed the orthodox approach. Thoracoplasty followed by a Schede and a decortication of the lower portions of the lung, if these were free of parenchymal disease so as to allow re-expansion and obliteration of some of the dead space.

TABLE 3
Treatment and Fate of Cavities Uncollapsed by Thoracoplasty, March 1947 to March 1948

Case	Sputum after thoracoplasty	Type of secondary procedure	Comments	Sputum at present
1 M	+++	Revision		---
2 O	+++	Revision		---
3 S	+++	Revision		---
4 F	+++	Revision		---
5 R	+++	Revision		+++
6 D	+++	Revision	To recent for final evaluation	+++
7 V	+++	Revision	Improved but no complete conversion	+++
8 Pa	+++	Revision	Sputum +++ after revision converted after cavernostomy	---
9 Re	+++	Cavernostomy		++
10 P	+++	Revision	Developed tuberculous wound infection and finally came to resection	---
11 Pe	+++	Revision	Sputum +++ after revision converted after resection	---
12 L	+++	Lobectomy	Excision after thoracoplasty resulted in conversion of sputum	---
13 T	+++	Pneumonectomy & Pleurectomy	Concomitant empyema	---
14 J	+++	Pneumonectomy	Extensive unilateral disease	---

The latter adjunct procedure has resulted in a considerable shortening of the time needed to obtain healing and closure of a pleurectomy wound

Thoracoplasty Failures

In every service handling the surgical aspects of the treatment of pulmonary tuberculosis there accumulates a residual group of patients in whom thoracoplasty has failed to bring about the arrest of their disease. Disappointed and discouraged these patients present an important problem and challenge, both psychological and therapeutic. During the one year period 14 such patients have been encountered (Table 3)

Numerically the most important group is the one that was selected for revision operations. Ten such patients have been treated by a modified type of thoracoplasty revision combined with an open intrapleural freeing of the lung and a fixation of the apex in a lowered position by either some plastic procedure utilizing a pleural flap or a muscle transplant taken from the pectoralis group. This type of procedure has been chosen because revision alone in cases who had a technically satisfactory thoracoplasty to begin with, has been shown to result in only questionable improvement over the preceding thoracoplasty.

The question arises for what reasons a revision with apicolysis would appear to be preferable to resection. The former procedure has been elected in this group of cases on the following basis. After the pleural space has been entered and the upper portion of the lung has been freed the operator is in a position to palpate the lung and to correctly evaluate the pathology present. The value of such first hand information cannot be over-emphasized. In a certain number of cases it became apparent that there was sufficient elasticity present in the parenchyma to allow important shrinkage of the lung after lysis had been accomplished. In addition to this, other factors are to be taken into consideration. First amongst these is the presence or absence of a well developed interlobar fissure and the distribution of pathology throughout the lung. The important question to answer is whether a lobectomy is feasible or whether the situation will not permit anything less than a total pneumonectomy.

There have been instances where the wide distribution of the pathology and the history of some disease in the contralateral lung militated against even a lobectomy and would certainly have precluded the resection of a whole lung. In this type of case we have preferred to settle for a revision with apicolysis and fixation of the freed apex of the lung in a lower position.

Of the group of ten patients having undergone this type of

Stomatitis and Dermatophytosis Coincident to Streptomycin Therapy

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Four cases of streptomycin stomatitis are presented together with three cases of eczematous dermatitis of the hands and feet coincident with streptomycin therapy, and attention is called to association of stomatitis with a vulvar mycotic lesion in one instance and concomitant stomatitis with severe trichophytoid lesions of hands and feet in another

While the over-all series of treatment with streptomycin at this institution embraces a period of 28 months and 130 cases, it is notable that the pharyngeal ulcers to be described occurred relatively rarely in this series. Recrudescence of *pre-existing* trichophytosis was observed while the patient was undergoing streptomycin therapy. In each of the severe cases of eczematoid dermatitis to be described, a pre-existing trichophytosis of the feet was noted. In the light of the history of previous fungus infection, it is perhaps not illogical to infer that streptomycin therapy tends, in some cases at least, to give impetus to the trichophytosis already present.

Case 1 Pharyngeal and vulvar ulceration. W C, a 22 year old white woman was admitted to Mississippi State Sanatorium on June 30, 1947. Admission diagnosis was bilateral, far advanced pulmonary tuberculosis. Auscultation revealed coarse, post-tussive rales throughout the right lung and expiratory wheeze over the subclavicular area. Coarse rales throughout left chest during both phases of respiratory cycle. Dullness to percussion was elicited at the level of the fourth rib anteriorly on right and an impaired note from the sixth to the ninth rib posteriorly on left side. Roentgenograms disclosed bilateral perihilar and mid-lung field infiltration, with fine feathery mottling of lung fields bilaterally almost through their entirety.

Streptomycin therapy was instituted on July 1, 1947, consisting of 2.0 grams daily parenterally and 0.5 gram by inhalation. A total of 85.0 grams was given. Blood counts, urinalyses and N P N determinations were done periodically throughout the course and were within normal limits.

Pharyngeal ulcers were noted on August 25, 1947 (after 78.0 grams had been given). The ulcers were initially observed on the anterior pillars, the buccal mucous membrane, sublingually and on the vermilion border of the lips. Initially, they appeared as white two to four millimeter vesiculations which within 36 hours broke down to form five to eight millimeter craters eventually covered with shaggy, dirty white membrane.

Small vesicles appeared at the corners of the mouth and broke down to form fissures

Smears taken repeatedly disclosed no specific organism. To prevent spirochetal infection, the membrane was removed from the ulcers and 10 per cent neo-arsphenamine in glycerin was applied topically followed by perborate mouth washes. Within 72 hours of the initial pharyngeal ulceration, vulvar ulcers following vesiculation were noted. Laboratory examination disclosed monilia and 2 per cent gentian violet was applied topically. Streptomycin was discontinued on September 5, 1947. Treatment of the lesions continued as above for 12 days. The ulcers, pharyngeal and vulvar healed. Re-institution of streptomycin (15 grams) resulted in recurrence of ulcers which again disappeared upon stopping streptomycin.

Case 2 Pharyngeal ulceration. R. F., a 21 year old white woman was admitted to this Sanatorium on June 4, 1948. Prior to admission she had right artificial pneumothorax for 14 months inadvertently re-expanded. Immediate pre-admission history was that of easy fatigability, persistent cough with moderate expectoration. Intermittent hoarseness for preceding 90 days. Small hemoptysis one month prior to entrance. Rhonchi were heard in sub-clavicular and inter-scapular areas on the right side. The findings were normal on the left side. A roentgenogram disclosed evidence of fibro-exudative lesion extending from apex to second inter-costal space anteriorly on right side. No unusual density was seen on the left side.

Bronchoscopy on June 17, 1948 revealed "considerable amount of granulation tissue near the carina. lumen of trachea reduced to about one-half its normal size" (Subsequent bronchoscopy revealed the right primary bronchus to be partially stenosed by granulation tissue). The patient was started on streptomycin on July 3, 1948. Thirty-one grams had been given by August 7 when vesiculations like those described in the previous case were noted (She had been requested to report all paresthesias in the mouth). Although streptomycin was discontinued immediately, the lesions went on to crater formation within 48 hours. Neo-arsphenamine topically was used as in Case 1. The lesions cleared in five days. On August 12 streptomycin was re-started in 1000 milligram doses. On August 14 (within 48 hours) vesicles and ulceration again appeared (Total of 0.75 gram given). Faucial, buccal, sublingual and vermilion border of lips were the sites involved. This time the ulcerations persisted 10 days.

Because a successive bronchoscopy disclosed the lesion (tracheal) to be progressing after an original regression due to the streptomycin, the bronchoscopist felt that streptomycin was the only recourse. Streptomycin was again administered on September 23, 1948. After 333.3 milligrams there was a return of vesicles, generalized capillary dilatation over the body-surface, peri-orbital oedema plus angio-neurotic oedema of the lips. The temperature was recorded at 102.4 degrees F. The patient complained of intense burning sensations over the entire body and paresthesia and burning in the pharynx. Pyribenzamine (500 milligrams) resulted in subjective relief from burning sensations. Erythema of body was reduced and oedema of the lips disappeared gradually. Only two 5.0 millimeter ulcerations in the pharynx were seen and these disappeared in 72 hours.

Case 4 Pharyngeal ulceration S D L, a 16 year old white female was admitted April 21, 1948 with moderately advanced disease with a pronounced exudative component Roentgenographically, soft mottling from the apex to the horizontal fissure was seen on the right side and a cavum one centimeter in diameter at the level of the first rib anteriorly Two one by one centimeter exudative lesions in the first and second intercostal spaces respectively appeared on the left side Right artificial pneumothorax was unsuccessful Streptomycin was begun on April 26 at daily dosage of one gram and continued until August 24 The streptomycin was discontinued at this time because of the appearance of pharyngeal ulceration as described in preceding cases At this time a total of 900 grams had been given An attempt to re-start streptomycin resulted in re-appearance of the ulceration Subsequent discontinuance of streptomycin resulted in healing of the pharyngeal lesions It has not been the writer's experience that pyribenzamine prevents a second appearance of pharyngeal ulcers, i.e., once streptomycin has been discontinued because of onset of ulcers, and is subsequently re-started In this case the sputum was converted and remains negative as of September 25, 1948, the roentgenograms had shown excellent clearing of the exudative lesion

Case 4 Pharyngeal ulceration A K M, a 34 year old white male was admitted on May 29, 1948 with history of persistent cough (three months) and minimal expectoration Chest examination disclosed no abnormal findings A roentgenogram revealed peribronchial infiltration in lower one-half of left lung field Sputum was Gaffky iv Bronchoscopy on June 17 disclosed tuberculous bronchitis of left lower lobe bronchus without visible ulceration

Streptomycin was begun April 21 with one gram daily After 870 grams on October 7, a shaggy white membrane was seen over the aperture of Stenson's duct which was treated locally with neo-arsphenamine Streptomycin was discontinued Smears cultured on Sabouraud's medium were uninformative The crater surrounding the opening of Stenson's duct healed in five days after discontinuance of streptomycin Concurrent sublingual and vermilion lip border lesions also healed The lesions re-occurred on re-starting streptomycin Successive bronchoscopies have revealed that the bronchial lesion in the left lower lobe has improved markedly

Case 5 Recrudescence of dermatophytosis W de L, a 40 year old white man was admitted on May 14, 1946 with positive sputum and an infiltrative lesion confined to left apex roentgenographically Left pneumothorax was instituted Ineffective closed pneumonolysis was done on February 3, 1947 Inasmuch as the cavity would not close, pneumothorax was abandoned and he came to three stage thoracoplasty begun October 27, 1947 and completed December 16

Between the first and second stages, the patient was highly febrile for several days A check film disclosed widespread apparently tuberculous disease on operative side Bronchoscopy at this time revealed no blockage of major bronchi Streptomycin was begun November 5, 1947 at 20 grams daily in hope of controlling disease in ipsilateral side and prevention of spread to contra-lateral lung The patient's temperature approached normal and a check-film showed marked clearing The second stage was done on November 25 and the third was finished as mentioned

The course of streptomycin was continued until 1450 grams had been given. At this time eczematous weeping lesions of hands were noted. Initially the lesions were vesicles which ruptured to liberate clear fluid. In later stages the overlying skin became undermined, sloughed and the corium was exposed. The skin sloughed from the terminal phalanges of the index, middle and ring finger of the right hand. The thumb had weeping lesions of lesser intensity. Boracic acid soaks, Lassar's Paste to the denuded areas plus touching up of ruptured vesicles with 2 per cent silver nitrate was accomplished. Streptomycin was discontinued at 1450 grams.

The aforementioned lesions did not abate in intensity for four weeks. Questioning and examination of the patient revealed trichophytosis of feet admittedly present eight years (Organism identified by laboratory examination). When the lesions were subacute, quinine bisulphate was used as powder. The lesions of the hands and feet were healed completely in eight weeks. This and the two succeeding cases had similar histories of co-existent dermatophytosis of the feet with comparable reactions under streptomycin therapy and are therefore listed.

Case 6 Recrudescence of dermatophytosis. P.B., a 42 year old white man was admitted to Mississippi State Sanatorium on April 16, 1948 with a diagnosis of far advanced bilateral pulmonary tuberculosis. Roentgenograms disclosed evidence of fibro-caseous disease with loculations, embracing the upper two-thirds of the left lung field. On the right side a 30 by 35 centimeter cavity was seen in the apex and fibro-caseous disease extending from the apex to the second intercostal space anteriorly. A tracheo-bronchial lesion was discovered on early bronchoscopy. Pneumothorax on the left side was unsuccessful (endobronchial lesion noted on right).

Streptomycin was begun May 26, 1948 with 10 gram daily. This was discontinued August 28 after 810 grams had been administered. On August 25 an eruption of vesicular nature was noted on the hands. The vesicles ruptured and proceeded to weeping eczematoid type lesions involving three digits on the left hand. Coincident dermatophytosis of feet was present prior to streptomycin therapy and exacerbated during the course of treatment. There was previous history of chemical (paint factory) dermatitis three years before. Remedial measures previously mentioned were used topically. Pyribenzamine was ineffective. In this case as in the fore-going, the existent dermatophytosis on the feet became worse during streptomycin therapy. At this point it must be mentioned that contact of hands and feet is unavoidable and is a factor. The emphasis, however, is on the recrudescence of the lesions.

Case 7 Pharyngeal ulceration and recrudescence of dermatophytosis. J.H.R., a 58 year old white man was re-admitted May 10, 1948 with far advanced bilateral disease. A complicating vocal cord ulcer and an epiglottic implant were the indications for streptomycin. The roentgenograms disclosed evidence of fibro-caseous infiltration of the upper one-half of both lungs and basal emphysema. Streptomycin was begun on May 17 at 10 gram daily, discontinued August 23 after a total of 920 grams had been given.

After 880 grams of streptomycin it was noted that a dermatophytosis of the feet (present for 12 years) was progressively worse. Vesiculations which ruptured to leave superficial slough were followed by beefy red

weeping lesions of both feet. The existent dermatophytosis of the toes spread to involvement of one-half of the dorsum of each foot. Treatment locally as outlined previously was ineffectual. Resort to 2 per cent aluminum acetate proved more efficacious. Pyribenzamine was given in doses of 200.0 milligrams daily for two weeks.

After 90.0 grams of streptomycin, pharyngeal ulceration as in previous cases was noted. Marked fissuring of the mouth borders was also noted as in the first case cited. Subjective improvement of hoarseness and objective improvement of epiglottitis and vocal cord lesions were noted. Streptomycin was continued until a total of 92.0 grams was given.

The dermatophytosis grew progressively worse with denudation and extremely slow re-epithelialization. The pharyngeal ulceration in this case progressed until the craters measured 8.0 millimeters in diameter. The objective in this case was achieved in that the epiglottic and vocal cord lesions healed. The pharyngeal lesions healed 18 days after onset (14 days after stopping streptomycin). The dermatophytosis healed 90 per cent after 12 weeks. Associated vestibular disturbance (vertigo) persists at present writing, nine weeks after streptomycin was discontinued.

Commentary

Observation of these complications of streptomycin therapy leads to the consideration of the following points: (1) Streptomycin reduces bodily resistance to pre-existing fungus infections (vid trichophytosis) giving added impetus to these entities. Close observation is indicated when giving streptomycin in these cases. (2) Caution is called for in administering streptomycin to women with vaginal tract fungaceous infestations of any degree (vid case 1). (3) Until further work with pharmaceuticals calculated to minimize streptomycin reactions, particularly stomatitis, proves efficacious, streptomycin had best be discontinued when such complications occur. Repeated efforts were made to re-start streptomycin in fractional doses with and without pyribenzamine to no appreciable avail.

SUMMARY

- 1) Four cases of pharyngeal ulceration occurring during streptomycin therapy are presented.
- 2) Three cases of recrudescence of pre-existing dermatophytosis are recorded.
- 3) One case was a combination of pharyngeal ulceration and vulvar ulceration.
- 4) One case represented combined pharyngeal ulceration and dermatophytosis.

RESUMEN

- 1) Se presentan cuatro casos de ulceración faríngea que ocurrieron durante el tratamiento con estreptomicina.

- 2) Se señalan tres casos de recrudescimiento de dermatofitosis pre-existente
- 3) En un caso hubo coexistencia de ulceración faríngea y vulvar
- 4) En un caso hubo ulceración faríngea y dermatofitosis

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Hydrothorax, Ascites, and Pelvic Endometriosis

Report of a Case

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The syndrome of ascites, hydrothorax, and benign ovarian fibroma has been well recognized since Meigs' classical report¹ in 1937. Others² have noted a similar picture in the presence of other types of ovarian tumors, twisted ovarian cyst, and uterine fibroids. Some³ contend, however, that the term "Meigs' syndrome" should be applied only if a solid benign tumor of the ovary is found.

We recently had occasion to study a young woman with pelvic endometriosis in whom pleural effusion and ascites directly followed laparotomy. The possible relation between this occurrence and Meigs' syndrome is of interest and we are reporting the case herewith.

The patient, a 32 year old white housewife, was first admitted to Emanuel Hospital, Portland, Oregon, on May 22, 1944. She had had rather severe menorrhagia and dysmenorrhea since the menarche at 14 years of age, and at the time of menses had noted gradually increasing pelvic pain on straining at stool, urinary frequency and dysuria, and anorexia which was sometimes associated with nausea and vomiting.

She had had scarlet fever at the age of five, and one year later a "severe kidney infection" lasting two or three months. In 1937 when six months pregnant she was hospitalized for eight weeks because of toxemia. Uterine hemorrhage due to placenta previa occurred, and she was delivered spontaneously of a stillborn baby six weeks after admission.

Physical examination in May 1944, showed her to be small but well nourished. The presence of a systolic murmur heard at the apex and mitral area was recorded at this time but not on any subsequent admission. Pelvic examination showed the uterus to be adherent posteriorly, little if any enlarged, but with marked bilateral nodularity, palpable chiefly on rectovaginal examination. This area posteriorly was intensely sensitive to palpation, particularly near the time of her menstrual periods. The induration was more pronounced on the left and here a sense of cystic enlargement could be elicited.

At laparotomy on May 23, 1944, the retroverted uterus was found to be rather densely adherent to the sigmoid colon. The appendix was involved in an endometrial growth and there were a few endometrial nodules on the uterine fundus and on the peritoneal reflection of the bladder anteriorly. The left ovary contained a small cyst. Subtotal hysterectomy, appendectomy, and removal of the left tube and ovary were performed. The pathologist, Dr. H. H. Foskett, reported endometriosis on the surface of the uterus, appendix, and left ovary. The latter contained a corpus luteum cyst. Endometrial hyperplasia with areas of

hemorrhage was present in the uterine canal Recovery was uneventful and the patient was discharged on June 4, 1944

In July 1944, she began to have dyspareunia and lower pelvic pain Rectal bleeding and discomfort on defecation occurred at the time of expected menses, and became more severe in January 1945 Vaginal examination showed numerous nodular growths in the cul-de-sac, one of which was about 4 cm in diameter She was admitted to the hospital on February 3, 1945, where 50 mg of radium was implanted in the cervical canal for a total of 2,000 milligram hours of radiation This therapy was carried out for the purpose of eliminating ovarian activity, which definitely was responsible for the continuation of the endometriosis process

Her pelvic pain and other symptoms were much less for the following year Early in 1946, however, monthly cramping pain again became severe, and urinary frequency, dysuria, urgency, and nocturia recurred, together with episodes of anorexia nausea, and vomiting

These symptoms led to her third hospital admission on July 10, 1947 Physical examination revealed a midline lower abdominal scar and tenderness in the left lower quadrant to moderate palpation The external genitals were palpably and visibly free of pathology The vagina was normal, but on rectovaginal palpation the utero-sacral ligaments were found to be intensely sensitive and slightly nodular, but much less indurated and smaller than on previous occasions No adnexal pathology could be determined It was felt that ovarian activity had not been completely abolished and that it was necessary that this be brought about in order to alleviate any hormonal effect on the endometrial lesion More radium therapy seemed inadvisable Deep x-ray therapy was ruled out because of a rather irritable bowel Hence surgical removal of the ovary seemed to be the reasonable and most logical choice Routine examination of the blood and urine was normal except for the finding of diacetic acid and occasional pus cells in the urine The blood serology was negative

Laparotomy was performed under cyclopropane-curare anesthesia on July 11, 1947 An adhesion between the omentum and upper abdominal wall was divided but no other adhesions or active endometrial lesions were evident The right ovary and tube were removed and the area peritonealized This ovary was situated rather high on the right lateral pelvis and was moderately adherent No other visible or palpable pathology was seen in the lower abdomen The upper abdomen was not examined

Examination of the specimen showed the tube to be normal There were a few areas of discoloration with scar formation and hemorrhage on the surface of the ovary Sections showed a number of endometrial transplants and several zones of pigment accumulation in the cortex There was also a small zone of fibroblastic proliferation containing a few small lymphocytic aggregations in the ovarian stroma Study of many sections did not reveal any evidence of ovarian fibroma or Brenner's tumor

The early postoperative course was marked by considerable nausea, vomiting, and generalized abdominal pain and distention On July 15th, the 4th postoperative day, the patient awoke short of breath Examination showed signs of a large right pleural effusion

Next day, 500 cc of clear fluid was withdrawn This contained 50,000

red blood cells and 700 white blood cells per cubic centimeter, of which 57 per cent were lymphocytes and 43 per cent polymorphonuclear neutrophils. The protein content was 0.96 per cent. Cultures of the fluid for tubercle bacilli and other organisms showed no growth. The centrifugated sediment was examined by the pathologist, who reported many lymphocytes, numbers of large mononuclear cells with hyperchromatic nuclei, others of fibroblastic origin, and a few hyperchromatic polynucleated cells. No definite tumor cells were found. About 1,800 cc of fluid was removed on July 18th, with marked improvement in her dyspnea. The cell count of this specimen was much the same as the first.

There was no reaction to the intracutaneous injection of 0.005 mg of PPD or to 1 mg of old tuberculin.

The patient left the hospital against advice on July 31, and came to the office in a wheel chair for thoracenteses. She continued to have a slight non-productive cough, temperature elevations to 99 degrees F, occasional pleuritic pain on the right, intermittent nausea and vomiting, episodes of mild diarrhea, abdominal soreness and distention, lumbar backache, weakness, and some urinary frequency, dysuria, and urgency. There was also recurrent upper abdominal pain usually half an hour after meals, associated with heartburn and belching. Her appetite remained poor and small doses of insulin were given before meals with little improvement. Therapy consisted of an amino acid concentrate, high protein diet, and symptomatic treatment of her abdominal distress. Perhaps unwisely, several oral doses of stilbestrol were given early in August because of troublesome nervousness and hot flashes. It was discontinued because she felt it increased her nausea.

Examination on August 8th showed her abdomen to be somewhat enlarged with flatness to percussion in the flanks and a fluid wave on palpation. She had gained weight from 97 to 103 pounds, presumably due to ascites. No edema of the face or ankles was present. The blood at this time contained 11.9 g of hemoglobin. There were 4.45 million red blood cells and 12,250 white blood cells per cubic millimeter. The differential white cell count showed 85 per cent neutrophils and 4 per cent eosinophils, polymorphonuclear leukocytes, 6 per cent lymphocytes, and 5 per cent monocytes. The sedimentation rate (Westergren) was 81 mm in 45 minutes. Urinalysis was negative except for 10 to 20 white blood cells per high power field in the voided specimen.

Thoracenteses were performed three times a week on the average until August 27, 1947. The amounts of thin, yellow, slightly turbid fluid withdrawn varied from 500 cc to 1,950 cc, and averaged 1,200 cc. There were 4,550 white cells per cubic millimeter on July 25, with 88 per cent lymphocytes and 12 per cent neutrophils. On August 15, the count was 1,225 per cubic millimeter with 65 per cent neutrophils, 20 per cent lymphocytes, and 15 per cent monocytes. The final specimen on September 26, contained only 300 cells per cubic millimeter with a similar differential count. The sediment obtained from centrifugating the pleural fluid was examined on several occasions. Each time, lymphocytes, eosinophils, granulocytes, monocytes, erythrocytes, and endothelial cells were found, but nothing indicating malignancy was reported.

The patient was fluoroscoped before and after each thoracentesis, and roentgenograms of the chest were made every two or three weeks. No lesion in the lungs was demonstrated.

On August 25, 3,500 cc of thin, clear yellow fluid having the characteristics of a transudate was removed from the abdomen. The path-

ologist reported the cellular elements to be like those in the pleural fluid. The blood serum protein was 7.2 per cent with 3.9 g of albumin and 3.3 g of globulin.

Two doses of Salyrgan-theophylline were given intravenously and restriction of salt and fluids was advised. After thoracentesis of 1,000 cc on August 27, her weight was 92 pounds. Her symptoms now gradually improved and she began to gain weight and strength.

The pleural effusion reappeared late in September, and what proved to be the last chest aspiration was performed on September 26, when 1,550 cc of fluid was withdrawn. Examination showed the liver edge to be 2 cm below the costal margin in the midclavicular line. There was some lower abdominal tenderness and dullness on the left side of the abdomen, but no free fluid was apparent. Subsequent fluoroscopy and roentgenograms of the chest showed the lungs to be normal.

During November and December 1947, there were occasional mild episodes of diarrhea, several hot flashes a day, infrequent twinges of pain in the right lower chest, and occipital headaches with nausea two or three times a week. Her weight was 101½ pounds and blood pressure 154/104. Examination of the heart and lungs was negative and the abdomen showed only slight tenderness in the lower portion. The blood on December 12 showed 10.5 g of hemoglobin and 3.98 million red blood cells and 6,750 white blood cells per cubic millimeter (80 per cent neutrophils). The sedimentation rate was 95 mm in 45 minutes. Urinalysis was negative.

When the patient was seen in June 1948, almost a year after her second laparotomy, she had no symptoms except for occasional two or three day episodes of mild lower abdominal pain once or twice a month, occasional loose stools, and infrequent hot flashes. Her weight was 110 pounds and her strength and appetite were good. There was slight lower abdominal tenderness, with "doughiness" on the left side but no apparent fluid, masses, or enlargement of the liver or spleen. The roentgenogram of the chest showed no abnormalities. The sedimentation rate was 22 mm in 45 minutes. A bromsulphalein test showed 6 per cent retention of the dye after 45 minutes.

An examination by an internist in February 1949, showed no evidence of recurrence of her ascites or hydrothorax. Her general condition had remained good.

Thanks are due to Drs. Foshett, Keane, and Conklin for their help with the management of this patient.

SUMMARY

In summary, this 32 year old patient had had prolonged symptoms of endometriosis, temporarily improved by subtotal hysterectomy and removal of the left tube and ovary in 1944 and by radium implantation in the cervix in 1945. At laparotomy on July 11, 1947, the other ovary (which showed endometrial implants) was removed. Four days after operation the patient developed a severe pleural effusion persisting for six weeks and requiring 20 thoracenteses. Ascites appeared a month after operation and one paracentesis was performed. Effusion into the peritoneal and right

pleural cavities ceased abruptly late in September, 1947, six weeks after laparotomy, and has not recurred

The basis for sudden onset and disappearance of these effusions is not known. A tuberculous etiology is quite unlikely in view of the negative tuberculin tests. The clinical findings do not suggest cardiac decompensation, hepatic or renal failure, or hypoproteinemia. Metastatic malignancy in the thorax and abdomen can also be ruled out. It is true that two cases with endometrial metastases to the lungs have been reported,⁴ but ascites and pleural effusion were not present in these patients. Our case is not presented as an example of Meigs' syndrome, but the similarity to reported instances of this condition is striking enough.

RESUMEN

En resumen, esta enferma de 32 años de edad, ha tenido síntomas prolongados de endometriosis temporalmente mejorada por la histerectomía subtotal y extirpación de la trompa izquierda y del ovario del mismo lado en 1944 y por la implantación de radio en el cervix en 1945. En la laparotomía en Julio de 1947, el otro ovario (que mostraba implantación endometrial) fue extirpado. Cuatro días después de la operación, la enferma tuvo un derrame severo pleural, persistiendo durante seis semanas que fue motivo de 20 toracéntesis. La ascitis apareció un mes después de la operación y se practicó una punción. El derrame dentro del peritoneo y de la cavidad pleural derecha cesó bruscamente a fines de Septiembre de 1947, seis semanas después de la laparotomía y no ha recidivado. La causa de la aparición repentina y la desaparición brusca de estos derrames no es conocida.

Una etiología tuberculosa no es justificable en vista de las reacciones negativas a la tuberculina. Los hallazgos clínicos no sugieren descompensación cardíaca ni insuficiencia renal o hepática ni hipoproteínemia. Una metástasis maligna en el tórax o en el abdomen también puede descartarse. Es cierto que otros dos casos con metástasis endometriales en el pulmón se han referido. Pero la ascitis y el derrame pleural no se presentaron en estas enfermas.

Nuestro caso no es presentado como un ejemplo de síndrome de Meigs, pero la similitud de esta condición con los casos referidos es bastante notable.

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Tuberculosis Control in Ohio State Reformatory

- (1) With Comparative Study of Two Year Periods.
- (2) With Survey of Penal Institutions in the United States and Canada.
- (3) With Recommendations for More Complete Control Measures.

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Introduction

In the August, 1947 issue of the Ohio State Medical Journal, the authors described the tuberculosis control measures followed at Ohio State Reformatory. The medical director of the reformatory initiated a tuberculosis control program at that institution January 1, 1944, by routinely x-raying all admissions and re-x-raying all for whom it was indicated, by isolating all active cases of tuberculosis, and by using collapse therapy in those for whom it was indicated. The statistical results of this control procedure was reported at the end of two years and a study of state needs, together with recommendations were made.

Since this is an institution of relatively short periods of incarceration, the average being 18 months, these control measures would readily manifest results. The statistics of another two year period have accumulated and have been compiled for comparison with those of the first two years.

For clarity in the present paper the control measures at Ohio State Reformatory are described again. Inmates upon admission to this institution are placed in isolation and while there are given a complete history, physical and psychiatric examinations and also an x-ray inspection of the chest. Those inmates who show need for further observation are followed as may be indicated and those who are found to have tuberculosis are placed in the hospital. The definitely active cases are isolated in separate wards and when they become non-infectious they are transferred to a convalescent ward. When the patients progress further in the cure they are placed on a convalescent range and move the run of an isolated section of the prison yard during certain specified times. They continue under hospital supervision and receive special diets, vitamins, and anti-anemic medication.

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While under treatment, the patients receive bed rest. Artificial pneumothorax, thoracoplasty, and other surgical collapse procedures are used in those cases in which it is indicated.

After the patients become apparently arrested and discharged to light outdoor assignments, they are called in at six week intervals for a review of temperature, pulse, and weight and x-rayed as may be indicated.

Continuation of Control Procedures of 1944-45

The above quotation also describes the control procedure followed during 1946 and 1947. A definite effort has been made to make all facilities available for control purposes as useful as possible. Tuberculosis was constantly kept in mind and patients were x-rayed and re-x-rayed as indicated. It was felt that a day by day consciousness of tuberculosis is better than routine x-ray surveys of six to 24 month intervals, if not integrated with a planned program. Routine surveys at intervals may be sufficient after a definite control procedure has been established in each institution with adequate provision for isolation, treatment, and rehabilitation.

Control Measures in Other Institutions

A survey of penal institutions in the United States and Canada was made. Seventy-three State, 21 Federal, and 10 Canadian penal institutions were sent a questionnaire covering the four phases of a tuberculosis control program. Answers were received from 55 State, 17 Federal, and six Canadian institutions. This is a representative group of institutions and should give some idea of the control measures in the penal institutions in general.

Procedures Used in Tuberculosis Case-Finding in Penal Institutions

Questionnaires, 104, Answers, 78

METHOD OF CASE FINDING	State	Federal	Canadian	Total
Physical Examination	44	15	4	63
Tuberculin Test	10	3	0	13
Fluoroscopic Examination	6	5	0	11
X-Ray, Small Film	6	8	3	17
X-Ray, Large Film	25	5	1	31
Sputum Examination	16	7	1	24

Fifty-four institutions answering the questionnaire stated they had a case-finding program, but in an analysis of the answers to all questions, it is apparent that only a few have a case-finding

program that is continuously, day by day, searching for new cases of tuberculosis. Physical examination which is inaccurate is the most frequent diagnostic procedure used. X-ray inspection by the large film technique is the next most frequent procedure used. This is used only when indicated and none stated it was used on all admissions.

Mass x-raying by the small film technique was used in 17 institutions. It was more frequently used in Federal institutions than State. It was used semi-annually to every two years and was generally brought in at the discretion of some outside agency. There was nothing to indicate that this procedure was integrated with any organized method of tuberculosis control within the institution. There are various other methods of case-finding in some institutions which also are not linked with a planned program.

Isolation Procedures Used in Penal Institutions

Questionnaires 104 Answers, 78

ISOLATION USED	State	Federal	Canadian	Total
Tuberculosis Ward in Penal Hospital	32	5	4	41
General Penal Hospital	2	0	0	2
Special Tuberculosis Hospital				
For Penal Patients	12	13	1	26

Forty-one institutions isolated their tuberculosis patients in a special ward in the general penal hospital. Two isolated their tuberculous in the general penal hospital. Twenty-six institutions had a special tuberculosis hospital for isolation of their patients. The federal institutions all send their tuberculous patients to the Medical Center for Federal Penal Institutions at Springfield, Missouri. Although the Federal Penal Institutions have the advantage of being able to remove their tuberculous cases to the Medical Center in Missouri, when diagnosed, there is nothing to indicate that the case-finding method in Federal Institutions is superior to that in State institutions except the more frequent use of mass x-ray surveys. Twelve State institutions and one Canadian had special hospitals for their tuberculous patients.

Upon closer inspection and analysis of the questionnaires in regard to isolation procedures in the different states it appears that in 23 states the tuberculous patients are isolated in the tuberculosis ward of the penal hospital. Not more than eight states have a special tuberculosis hospital for the penal tuberculous. Five states send their tuberculous patients to the State Sanatorium. Two states have a large special ward in the hospital of

one of their penal institutions Two states put their tuberculous patients in the general penal hospital An occasional institution will obtain a parole for a tuberculous patient and return the patient to the county authority for treatment

Treatment Procedures Used in Penal Institutions

Questionnaires, 104, Answers, 78

PROCEDURES	State	Federal	Canadian	Total
Bed Rest	41	9	5	55
Pneumothorax	17	1	2	20
Thoracoplasty	10	0	1	11
Phrenic	11	1	2	14
Pneumoperitoneum	9	1	0	10
Intrapleural pneumonolysis	5	1	0	6
Extrapleural pneumonolysis	7	0	1	8
Dietary Consideration	28	1	5	34

Bed rest is commonly used in the treatment of these cases in the various institutions Many give their patients special dietary consideration Collapse procedures are occasionally used and probably to the extent that specialists or consultants are available or special tuberculosis hospitals

Only 20 answering stated they had a rehabilitation program and only four institutions stated they planned a program This appeared to be the weakest link in the tuberculosis control chain, and quite naturally would be the last developed program

Statistics for 1946-47 at Ohio State Reformatory

From January 1, 1946 to January 1, 1948, the same case-finding program was followed as in the two previous years During this two year period, 2424 commitments had routine chest x-ray inspection with subsequent follow-up of those in whom it was indicated Of these, 1678 inmates were white and 746 were colored Fifty-two cases were diagnosed as having tuberculosis of which 40 were active and 12 healed Of these, 33 were white and 19 were colored Four white had pleurisy with effusion, and one white and three colored had primary tuberculosis

Of the total x-rayed, 2.1 per cent had tuberculosis in some form excluding healed primary lesions Active tuberculosis 1.65 per cent, inactive tuberculosis 0.49 per cent Thirty-three or 1.96 per cent of the whites had tuberculosis of which 27 or 1.6 per cent had active tuberculosis Nineteen or 2.57 per cent of the colored had tuberculosis of which 13 or 1.74 per cent were active Six or 0.3 per

cent of the white and six or 0.8 per cent of the colored had inactive tuberculosis.

The following tables give the number and percentage of the active and healed cases of tuberculosis in the different classifications and by race.

White Inmates				
CLASSIFICATION	ACTIVE		INACTIVE	
	No.	Per cent	No.	Per cent
Minimal	13	39.1	1	12.12
Moderately advanced	8	21.21	1	3.03
Far advanced	1	3.03	1	3.03
Pleurisy with effusion	1	12.12	0	0
Primary	1	3.03	0	0
TOTAL	27	81.82	6	18.18

Colored Inmates				
CLASSIFICATION	ACTIVE		INACTIVE	
	No.	Per cent	No.	Per cent
Minimal	2	10.53	5	26.32
Moderately advanced	7	36.84	1	5.26
Far advanced	1	5.26	0	0
Pleurisy with Effusion	0	0	0	0
Primary	3	15.79	0	0
TOTAL	13	68.42	6	31.58
GRAND TOTAL	40	76.92	12	23.08

Comparison of Statistics of Years 1946-47 with those of 1944-45

	1944-45	1946-47
Total Inmates	2419	2424
White	1665	1678
Colored	754	746
Active Tuberculosis (White)	29	27
Active Tuberculosis (Colored)	23	13
Inactive Tuberculosis (White)	28	6
Inactive Tuberculosis (Colored)	37	6
Active Rate (White)	1.74%	1.67%
Active Rate (Colored)	3.05%	1.74%
Total Rate	3.67%	2.1%

In a comparison of the above two year periods, it is noted that there is little difference in the total number x-rayed, the number of whites, and the number of colored. There was a definite drop in the number of active cases of tuberculosis in both white and colored, and a marked drop in the number of inactive cases of tuberculosis in both races. The active cases in the white population dropped from 1.74 per cent to 1.67 per cent and in the colored population from 3.05 per cent to 1.74 per cent. The total rate dropped from 3.67 per cent to 2.1 per cent.

For diagnostic confirmation of the above tabulated cases, it is well to state that all admissions to this institution received a patch tuberculin test and that all cases in which a diagnosis of tuberculosis is considered, have sputum examinations made. These patch tests were not repeated nor checked by any other skin testing method. Facilities were not available for cultures and guinea pig inoculations and gastric washings were not done. Only the routine sputum examination was done.

In the far advanced active cases of tuberculosis, 100 per cent had positive sputum and 100 per cent were non-reactors to the tuberculin patch test. Forty per cent of the moderately advanced active cases had positive sputum and 60 per cent reactors to tuberculin. None of the presumptive minimal active cases had positive sputum and 60 per cent reacted to tuberculin. No guinea pig inoculations, cultures, or gastric washings were done on the cases of primary tuberculosis or pleurisy with effusion.

There has been a satisfactory response to the tuberculosis control program that has been in effect here the past four years, the most marked results having been obtained in the colored race and satisfactory results in the white race. Although definite and satisfactory results have been obtained in the practice of this control program and in reducing the cases of tuberculosis from 3.6 per cent to 2.1 per cent, further improvement should and could be made. There has been a definite reduction in the number of cases of extrapulmonary tuberculosis, in the cases of primary tuberculosis, and in the cases of pleurisy with effusion. This probably means the contact rate has dropped.

In the first two years from 1944-45, the cases of tuberculous tracheo-bronchial glands were classified with the cases of pulmonary tuberculosis. In the present study, they were classified as primary tuberculosis and their pulmonary manifestations as extensions of the primary infection. There has been a definite reduction in the number of cases of tuberculosis of the tracheo-bronchial lymph glands in the last two years.

The most marked reduction in the number of cases of tuberculosis in both white and colored, was in the cases of inactive

tuberculosis. We can offer no satisfactory explanation why there is so much greater reduction in the number of such cases unless it is due to the short period of two years which this study covers.

Recommended Control Measures

It was recommended in the previous report that a penal sanatorium be built in Ohio sufficient in size to meet the needs of the State and that an active case-finding program be developed in all the penal institutions and the active cases of tuberculosis be transferred to that institution. This same program adapted to the needs of the individual States and modified to fit into existing facilities is recommended for adoption.

This survey of penal institutions in the United States and Canada, which at best can only be superficial, suggests that probably only the larger and most populous States could practically have a penal tuberculosis hospital. Some of the smaller States may have a large special tuberculosis ward in a penal hospital near a metropolitan area where the services of specialists and rehabilitation facilities may be had. Some States may develop special facilities in one of the State Sanatoria. A few institutions in the sparsely populated Northwestern States and in Maine stated they had not had a case of tuberculosis. These States probably could adequately take care of their patients in a State or County institution where a few special rooms are developed for penal patients. The Federal institutions apparently have facilities for isolating their tuberculous patients in the Medical Center for Federal Penal Institutions at Springfield, Missouri.

Until such time when adequate hospital facilities may be had, the incidence of tuberculosis in penal institutions may be reduced by a tuberculosis control program as outlined here. It is a plan that could be followed in any institution that could have the occasional services of a chest specialist. This program would require little extra help or cost.

It is recommended that all penal institutions initiate a tuberculosis control program with the facilities at hand. All admissions to penal institutions should have chest x-rays together with the other admission examinations. The initial x-ray would preferably be by the large film technique. Inmates who present themselves to the clinic or physician for illnesses in which the diagnosis is not obvious, should be screened for tuberculosis. Suspects should be kept under observation. The institutional staff should have chest x-rays upon hiring, and subsequently at intervals best determined by future experience. Active cases of tuberculosis should be placed in bed in a special section of the penal hospital with the open cases together and the negative sputum cases in a sepa-

rate ward The different types of collapse therapy should be used as indicated When the cases progress in their cure to the point when they may be given privileges of mild forms of exercise, they should continue under hospital supervision After discharge from the hospital, they should be called in at six week intervals for weighing, recording of temperature and pulse and examination If there is any evidence of reactivation, the patient should be placed in bed again

After the above control program has been established, survey of the institution by the small film technique may be begun This may find those occasional cases that are missed by the above method In this institution, there has been one mass x-ray survey* since the above control program was initiated Not a single new case was found Survey by the small film technique may be made at 6 to 12 month intervals or as may be indicated by future experience

The above may be carried out in any institution and the tuberculosis rate definitely reduced Also, each State should plan a tuberculosis hospital program for the penal tuberculous Only in the larger States would it be practical to have a penal tuberculosis hospital In other States, a special section in a State, County, or Municipal Sanatorium may be prepared for penal patients In other States where there is a large penal hospital, a special section of this may be suitably used for isolation of the tuberculous

When the time comes that an adequate number of beds are available for the penal tuberculous, this should not alter the case-finding program This should continue as before The tuberculosis hospitals would only take the tuberculous out of the prison population

It is planned that BCG vaccine be given a trial as a control method here If successful, it should be a valuable adjunct to the procedures already used

It is also planned that the routine use of intradermal tuberculin and histoplasmin skin tests be added to the tuberculosis control program here as a matter of correlating the incidence of calcification with tuberculin and histoplasmin reactions

*A second mass x-ray survey with the 70 mm film May 23 to 27, 1949 did not disclose any new cases of tuberculosis

CONCLUSIONS

1) An active tuberculosis control program has been followed in this institution for four years with reduction in the incidence of tuberculosis from 3.67 per cent to 2.1 per cent

2) The tuberculosis control program in 78 penal institutions in

the United States and Canada is inadequate in almost all institutions answering the questionnaire

3) All institutions could markedly decrease the incidence of tuberculosis by actively engaging in a tuberculosis control program with the facilities available

4) The basis of any control program is built around a place for isolation and treatment. In large populous States this may be a penal tuberculosis hospital. In smaller States, it may be a penal section in a State or County tuberculosis hospital. In other States, it may be a tuberculosis division of a large penal hospital

CONCLUSIONES

1) La aplicación de un plan activo para el control de la tuberculosis en esta institución por cuatro años con reducción en la incidencia de tuberculosis de 66 a 21 por ciento es presentada

2) El programa de control de la tuberculosis en 72 instituciones penales en los Estados Unidos y Canadá, es inadecuada, en casi todas las instituciones que contestaron el cuestionario

3) Todas las instituciones podrían hacer descender la incidencia de la tuberculosis francamente estableciendo un programa de control con las facilidades que tienen a su alcance

4) Las bases de cualquier plan de control deben construirse alrededor de la existencia del lugar de aislamiento y tratamiento. En los grandes estados muy poblados, puede haber una institución penal o un hospital penal para tuberculosis. En estados más pequeños, podría ser una sección penal en un hospital de tuberculosos del estado o condado. En otros estados puede haber una división de tuberculosis en un gran hospital penal

REFERENCE

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Tuberculosis Among Indians of the United States

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The most outstanding health problem among the Indians of the United States today is the exceptionally high incidence of tuberculosis. Such a situation creates a serious threat to the acculturation and economic development of the Indian race and constitutes an important reservoir of infection for the non-Indian population of the country. While significant strides have been made to control tuberculosis among Indians, chiefly through efforts of the United States Bureau of Indian Affairs, the accomplishments to date have been far from satisfactory. Tuberculosis among Indians is just as amenable to proper measures of prevention and cure as it is among the white population. The conscientious application of effective control methods will not only aid materially the advancement of the Indian people, but also result in greater progress in tuberculosis control among the general population.

Extent of the Problem

The popular belief that Indians at the time of the discovery of America had a remarkable vitality and freedom from disease is confirmed by the writings of early explorers, colonists, doctors, and missionaries. There is no evidence to show that tuberculosis existed prior to that time. Hrdlicka¹ declares "As yet no bones of undoubtedly pre-Columbian origin have been found that show tuberculous lesions, and such lesions are very rare in Indian bones dating from the period of the earliest contact with the whites." Scrofula and consumption were observed among the Indians of the Northwest as early as 1633 by Jesuit priests. Evidence from the literature indicates that in the early days of colonization the prevalence of tuberculosis among the Indians was no greater than among the whites, and perhaps not as great.² Following closer contact with whites, with restrictions to army posts and reservations, the Indians began to develop and spread the disease with appalling rapidity. Early reports do not give any accurate or reliable information regarding mortality and morbidity rates, but more complete observations have dated from the establishment of the Indian Medical Service as part of the Bureau of Indian

Affairs in 1873 The records indicate that tuberculosis continued to steadily increase until the latter part of the nineteenth century reaching an average morbidity rate of 23 per cent in 1884.³ Hrdlicka⁴ investigated in 1908 the morbidity of tuberculosis among a group of 107,000 Indians. He recorded 2,836 instances of the disease which were divided as follows: 1,038 pulmonary tuberculosis, 208 tuberculosis of the bones and joints, and 1,590 tuberculosis of the lymph nodes. It was found that the tribes which had the longest contact with the whites were the most seriously affected. The morbidity rate far exceeded that noted among the white population of that period.

In 1912 the United States Public Health Service made a comprehensive survey of infectious diseases among the Indians.⁵ During the survey, 39,231 individuals, or approximately one-eighth of the Indian population, were examined. The tuberculosis morbidity rate for this group was 3.5 per cent, and considerable variation was found among the different tribes. The incidence was lowest among the New York tribes with a rate of only 1.3 per cent and reached as high as 32.7 per cent among the Palutes of Nevada. The mortality from tuberculosis for the entire group was 506 per 100,000 population. It is interesting to note that during the same year the Bureau of Indian Affairs reported a total of

TABLE 1

YEAR	Tuberculosis Deaths per 100,000 Indian Population (compiled by Bureau of Indian Affairs)	Tuberculosis Deaths Per 100,000 General Population (U. S. Census Vital Statistics)
1912	1,040	145.4
1913	971	143.5
1914	919	141.7
1916	640	138.4
1918	630	149.8
1920	608	113.1
1923	439	91.7
1930	354.6	71.1
1939	265.1	47.1
1940	264.3	45.8
1941	275.8	44.5
1942	259.2	43.1
1943	206.2	42.6
1944	268.2	41.3
1945	211.9	40.1

7,886 cases of tuberculosis from a group of 58,266 Indians examined, an incidence of 13.5 per cent, and a death rate of 1,040 per 100,000.⁶ Such paradoxical results denote inadequate and inaccurate means of study and reporting due in part to the limitations of examinations. Although the above findings cannot be accepted as conclusive, sufficient evidence was accumulated during the Public Health survey to convince the investigators that tuberculosis was much more widespread than among the white population.

Since 1912 there has occurred a definite trend towards lower mortality and morbidity rates. The decline in mortality from tuberculosis is indicated in Table 1, which compares the rates among the general population of the United States with the Indian population.

The Bureau of Indian Affairs established in 1929 a system for the routine collection of reports of mortality rates, and data subsequent to that time are much more reliable. Encouraging as these statistics are in depicting a great reduction in deaths from tuberculosis, they also show rates of approximately five times that noted among the general population.

While these figures on mortality rates are a crude measure of the overall incidence of the disease, a more complete picture is obtained from morbidity rates as determined by clinical and x-ray surveys. In a ten-year series of clinical examinations by the Bureau of Indian Affairs, the rate decreased from 16.2 per cent in 1911 to 12.1 per cent in 1920.⁷ The average number of annual examinations was 64,543, or about one-sixth of the population. In surveys made from 1927 to 1933, the percentage of Indians examined which were found to have tuberculosis varied from 25 per cent of the Chippewas in Minnesota to 2 per cent of the Santees in Nebraska, with an average incidence of 10.1 per cent.⁸

Aronson,⁹ working with the Office of Indian Affairs, initiated in 1935 a program for the study of tuberculosis among Indians. The extent of tuberculous infection and disease was determined in certain areas where BCG vaccine was later to be evaluated in the control of tuberculosis. Aronson and his group tuberculin-tested 8,420 Indians of the Pima, Shoshone, Arapahoe, Sioux, and Alaskan tribes from 1935 to 1937. The incidence of positive reactors was over 50 per cent at 10 years of age and rose rapidly with increasing age, reaching approximately 100 per cent of individuals 25 years of age or above. It was shown that the percentage of positive reactors among Indians exceeded that previously noted by him among the negroes in rural areas of some of the southern states and among the whites in rural areas of Michigan. Roentgenological examinations of the chest were made during 1936 and 1937 of 16,046 Indians, who composed a significant sample of the

general population in each tribe. The incidence of pulmonary tuberculous lesions of clinical significance was lowest among the Pima Indians with 1.1 per cent and highest among the Alaskan Indians with 6.9 per cent with an overall average of 5.2 per cent.

Lower incidences in recent years are reported by Dahlstrom,¹⁰ who is conducting a series of mass X-ray surveys among Indians of the United States. He summarizes his findings (Table 2) on the occurrence of significant pulmonary lesions characteristic of tuberculosis as based on roentgenological examinations. In comparing these results with those obtained among mass surveys of the general population, it is evident that the incidence of tuberculosis as observed by roentgenological examinations of the chest, is significantly higher among the Indian than that found among the general population.¹

Cause of the Problem

Because tuberculosis has so widespread among the Indians, it has been assumed by many that they have a racial susceptibility to the disease and develop the more fatal, progressive types of tuberculosis. Most authorities who have observed and studied the disease among Indians have concluded that Indians as a race are not peculiarly susceptible to tuberculosis and develop the same type of disease in the same manner as has been observed among the white population. Allen, after reviewing the roentgenograms of Oklahoma Indians, noted that "comparatively healed lesions are often

TABLE 2

Year Surveyed	Location of Survey	No. of Indians Examined	No. of Tuberculous Lesions	Per Cent
1949	Apache, Arizona	3,170	7	2.0
1945	Crook Creek, South Dakota	512	12	2.4
1945	Tongah, Wisconsin (County Survey)	89	—	—
1945	Zuni, New Mexico	127	23	3
1945	Wind River, Wyoming	616	2	1
1946	Winnebago, Nebraska	168	16	1.1
1946	Sisseton, South Dakota	1,079	1	3
1946	Red Lake, Minnesota (State Dept. Health Survey)	1,022	67	—
1947	Pine Ridge, South Dakota	2,500	92	3.2
1947	Rosebud, South Dakota	2,659	54	2.1
1948	Navajo, Arizona (as of Oct.)	1,069	647	4.6
	TOTAL SURVEYED	29,487	1,028	3.2

noted and lesions in which the healing process is taking place are more frequently noted." Among these cases of presumable tuberculosis, the majority received no treatment and had no history of symptoms, indicating that natural healing takes place in Indians as well as whites. Alley has observed exceptionally few rapidly advancing lesions among sanatorium patients and finds that Indians respond very well to treatment. Aronson¹³ states that fibrosis and calcification are common and that the disease in many instances runs a long chronic course, even in the moderately or far advanced cases. He is also of the opinion that tuberculosis among Indians has undergone a change in character, and that there is much less of the extrapulmonary forms previously seen. As noted above, Hrdlicka¹⁴ found in 1908 that over 63 per cent of tuberculosis was extrapulmonary in nature. Indian Medical Service physicians have observed fewer instances of extrapulmonary forms of tuberculosis than formerly. These workers find no significant difference between the course or character of tuberculosis in Indians as compared to whites. Apparently the same defense mechanism operates in both Indians and whites, and immunological or racial factors play only a minor, if any, role in the cause of the high prevalence of tuberculosis among Indians.

The underlying economic and sociological conditions are perhaps more important. An evaluation of these conditions cannot be attempted without some understanding of the Indian people and the changes in environment which they have undergone. The advent of the whites created a struggle for existence that was fertile soil for the seeding and dissemination of tuberculosis. With the exception of some southwest Indians, the more than 200 tribes lived a nomadic existence in pre-Columbian times. The subsequent exploitation of the country determined their confinement to areas set aside as reservations under Federal control. In these restricted areas, they found it difficult to adjust to sedentary living and to a change in cultural pattern. Their roving life of former days dictated temporary shelter only large enough to protect the family unit against the elements. Adequate dwelling space, sanitary ways of living under crowded conditions for indefinite periods, and balanced diets were not effective parts of the economy pattern. The nomadic way of life in a bountiful land provided for them naturally. So when doomed to reservation life without sufficient experience of living under these conditions, they merely did the only thing they knew how to do—erect a place to live just large enough to protect them against the elements, dispose of their refuse without regard to its effect on the health of the family and community, and eat whatever was at hand without concern for any special preparation that might

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preserve its nutritional value. This gap is only a part of the total cultural lag and economic maladjustment which left them prey, as it will any group of people similarly afflicted socially and economically to the ravages of tuberculosis. Such adverse conditions were conducive to massive and continuous exposure to the disease and resulted in universal infection approaching epidemic proportions.

The Federal Government in virtual control since 1821 has done little to bring the Indians to a level in living conditions comparable to that of the general population. Its appropriations to the Bureau of Indian Affairs have always been meagerly. The main resource of the Indians was and still is land which has been so reduced in acreage that there does not now remain enough to support them at an income level sufficient to provide proper home life and living conditions. Not endowed by training or habit with inadequate credit and meager assistance in land use education they continue to exist in rural slums. In addition they are beset by exploiters of the land in the modern sense, coupled the Bureau of Indian Affairs with its curtailed budget, are not able to keep pace with the need for both youth and adult education and rehabilitation in the areas left to them. The efforts of normal health. The resultant poverty has an important, and direct, influence on the health of the Indian population by allowing inadequate housing space insanitation, and malnutrition to exist.

Murphy's statement that "The spread of the disease is primarily fostered by conditions existing in the homes," is unfortunately quite correct, for such conditions do have close correlation with the amount of tuberculosis among Indians. The average dwelling is built of clay, reeds, stones, or logs found in the immediate vicinity. The floors are usually made of dirt and proper ventilation is lacking. Frequently extremely ill patients are found living in a small one-room cabin with no, or very little, window space. Overcrowding is the rule with two or more generations living in close proximity in the same household. Young children subjected to such an environment cannot avoid infection with tuberculosis. Drinking water is obtained from wells, springs, streams, or irrigation ditches, and often is contaminated from domestic sewage. In many instances, the water must be transported from great distances and the supply may be limited, making difficult personal and household cleanliness even if the Indians were so inclined.

The influence of living conditions on the incidence of infection is well demonstrated by Aronson.¹⁶ He found in 1936, on the Rosebud Reservation in South Dakota, that 79 per cent of the children

attending the government and mission boarding schools had positive tuberculin reactions, whereas only 32 per cent of the Indian children attending the public schools so reacted. The Indian children in the public schools came from homes comparable to those of the neighboring white population, while the boarding school children came from the more crowded poorly housed families living under conditions similar to those in urban slums of the larger cities. In addition one must consider such factors as overcrowding and inadequate facilities in Indian boarding schools, where the children live in close association all during the school year, which may lend themselves to easier spread of infection. Ferguson¹⁷ further illustrates the relationship of living conditions to tuberculosis by showing a decreased death rate among the Indians of the File Hills Demonstration Colony in Saskatchewan, Canada comparable to that of the surrounding white population. These Indians lived under conditions similar in every way to those of the whites. However, those living under conditions typical of reservation standards did not have such a decrease.

The diet of the average Indian is not balanced and is deficient in many respects. Milk and fresh vegetables are seldom used, and most meals are poorly prepared. In general fats and carbohydrates are proportionately in excess, although certain groups subsist on meat almost exclusively. The Bureau of Indian Affairs has in the past issued rations of bare necessities, but now provides only the needy ones with funds to purchase food as they desire. Unfortunately, the food is improper from the standpoint of quality, quantity, and variety, and malnourishment and a debilitating state of health often result, making the Indians predisposed to the development of all diseases, including tuberculosis.

Lack of sanitary facilities on the reservation and in the homes is usually encountered. In addition, there is frequent disregard for the most elementary principles of personal hygiene and sanitation. Imbued with the primitive conceptions of the medicine man, the Indians have not readily accepted the idea that tuberculosis, and other diseases, are caused by invisible germs and that these germs may be present in healthy appearing individuals. They have not had sufficient exposure to health education to enable them to understand fully the factors involved in health and disease. Language difficulties and an inherent native reticence make them somewhat apprehensive of non-Indian health workers when health education programs are carried out.

Many social habits and tribal customs, which are a vital component of the structure of reservation life, contribute much to the spread of tuberculosis. The sick are visited freely without

regard to the condition of the patient. Indians frequently gather together for ceremonial and feasts where the ordinary facilities for proper sanitation are absent. At such times there is little concern for sanitary measures, and both sick and well intermingle freely. Individuals with active tuberculosis present in these groups transmit their infection readily into healthy families.

Inadequate medical care in many areas results in ineffective control over tuberculosis. An insufficient number of sanatorium and hospital beds prevent the isolation of all active cases, endangering the health of others in the community. The Federal Government, hasty to help downtrodden people of foreign lands, allows only a meager appropriation to the Bureau of Indian Affairs for medical services. In many cases it has been impossible to detect tuberculosis until it has totally incapacitated the individual and he comes to the attention of the medical profession too late for any beneficial therapy. Because medical care is not freely accessible to many Indians on various reservations, they hesitate to consult physicians until dire emergencies arise, making control of tuberculosis difficult and unsatisfactory.

Control of the Problem

In determining the causes of the high incidence of tuberculosis among Indians no single factor can be isolated. They are all interwoven with and dependent upon, one another. Consequently, our approach to the control of the problem involves the integration of many activities. Much has been contributed toward the control of tuberculosis among Indians not only by the Bureau of Indian Affairs, but also by the United States Public Health Service, National Tuberculosis Association, and various private organizations. The Bureau of Indian Affairs is attempting to meet the problem as part of a general health program instituted in the early part of 1947.¹⁸ As evidence of its activity, mobile photo-fluorographic units are now in operation conducting mass surveys on various reservations, and BCG vaccination has been introduced in certain areas. Fundamental control measures which have been so effective among whites are being applied in many instances. The spirit which animates this work is worthy of commendation and encouragement, however, the program now inaugurated is limited by lack of sufficient funds and needs further impetus to achieve ultimate control of tuberculosis.

First of all, there is urgent necessity for the immediate improvement of the economic status of the Indian before we can secure any definite and lasting results in controlling tuberculosis. Any improvement in health will be greatly accelerated by enabling the Indians to earn a decent livelihood and thereby achieve a

better standard of living The policy of the Bureau of Indian Affairs during the past 15 years has been to establish a self-supporting economy among the Indians They have been encouraged to accept more responsibility over their own affairs Eventually it is expected that the Indians will assimilate into the general population and take their place in the national framework But it is obvious that they must first be brought up to the standards of the general population, economically and otherwise The majority of Indians derive their income from agricultural pursuits, including livestock raising, but there is not sufficient productive land to provide even a mere subsistence economy It is necessary that the Indians be encouraged to protect and develop their resources, especially lands, and adding to them wherever possible With overpopulation accentuating the problem, the land must be used to the fullest productive capacity, and, at the same time, the excess population dispersed into industry On the reservations where feasible, the Indians should be encouraged to engage in craft industries which have a definite functional value in American life The American public should aid Indians to adjust to off-reservation employment when such opportunity exists Fortunately, Indians may obtain loans from a revolving fund set up by the Bureau of Indian Affairs for use by the individual or by the tribe or corporation, and this has met with considerable success A further discussion of the problem of economic rehabilitation is beyond the scope of this paper, however, the need for its solution cannot be overemphasized Until this is done, tuberculosis control programs will help, but the control will not be general as the poverty of the Indian people will keep fertile the media from which the disease keeps coming to the surface

Sanitation has perhaps been the most neglected phase of the general health program in the past It is recognized, of course, that any great amount of structural changes in health conditions must await improvement in the financial status of the Indians Nevertheless, much might be accomplished by an intensive program of health education and directing attention towards methods of prevention As with other economically depressed groups, the Indians must be taught how to live properly, how to prepare food to obtain the utmost nutritional value, and most important of all, how to combat the spread of disease It is necessary that the instruction be presented in a manner understandable to them, whether it be by lectures, films, bulletins, or demonstrations The Indian community offers in many respects an ideal setting for cooperative enterprises by health workers with other groups for the betterment of health with agricultural agents for the promotion of proper food and livestock raising, with home demon-

stration agents for the improvement of home conditions, with social welfare workers for aid to the more destitute families, with educators for health instruction of school children, and with the Tribal Council itself to bring the Indians into the scheme of organization for health. Murphy¹⁸ is of the opinion that, "The Indian children will be the best promoters of new ideas in the home, and will be able through the training received at school to advance materially all efforts along health lines. The education of younger Indians will be the quickest and most effective means of disseminating knowledge as to the nature of tuberculosis and best means of prevention and cure. In recent years the returned war veterans and war workers have added some contribution toward informing the family group about proper health measures. Every avenue of educational approach must be tapped in order to establish in the Indians a community concept of the disease. For, only when they develop an interest in the tuberculosis problem and understand its importance will the Indians cooperate fully in its control.

The most immediate phase of the control program is the use of comprehensive case finding surveys to locate the sources of tuberculosis on the reservation and the provision of their hospitalization. At the present time, the Bureau of Indian Affairs is employing the photofluorographic portable x-ray unit on some reservations. Such efforts should be given encouragement and financial support so that a significant proportion of the Indian population can be reached in a relatively short time. Because the Indian groups are so small and well localized on reservations, large numbers of the people are easily accessible for examination. In these ideal survey centers, concerted programs can be carried out on an extensive scale rapidly and at little cost. By this means, Indians who show indications of tuberculosis on roentgenograms can be studied further to determine the diagnosis, and if found to have active disease, they can be segregated immediately so as to remove the sources of infection from the rest of the population. It is obvious that the value of the case finding surveys depends on the completeness and adequacy of the follow-up study. Well equipped clinical and laboratory facilities are necessary for accurate diagnosis. Careful examination of all contacts is an important part of the control program.

Although the status of BCG vaccination has not been definitely established in control programs of the past, increasing evidence of its value among Indians has been shown. Aronson²⁰ investigated the use of BCG among a group of Indians of the United States and Alaska since 1935. It was administered to 1,551 Indians ranging in age from less than one year to 20 years, and at the same time

1,457 Indians of comparable age and living under the same conditions served as controls. They were followed over a period of nine to eleven years, and 6 deaths from tuberculosis occurred among the vaccinated group while 53 deaths from tuberculosis occurred among the controls. The mortality rate per 1,000 person-years of observation was 0.4, and 3.5 for the vaccinated and controls, respectively. Also a group of 123 newborn infants was vaccinated and 139 newborn infants served as controls. The infants were observed over a period of six to eight years, and no deaths have occurred from tuberculosis among the vaccinated, while among the controls 4 have died from tuberculosis. Aronson further found that roentgenologically demonstrable lesions having the characteristics of primary tuberculosis occurred in 22 of the vaccinated and in 120 of the controls. Minimal lesions of reinfection type, progressive lesions and miliary and extrapulmonary lesions of tuberculosis were found in 21 of the vaccinated and 93 of the controls. These results indicate that BCG-vaccinated Indians do have lowered mortality and morbidity over a fairly long period of observation. Because this evaluation has demonstrated that BCG may be used effectively as an immunizing agent, the control program should embody a vaccination plan whereby tuberculin negative individuals will receive BCG vaccine. The Bureau of Indian Affairs began the vaccination of 600 Indians in Alaska in the summer of 1948. Widescale vaccination of tuberculin negative children in the Indian boarding schools is now being initiated among Indians of the southwest and Dakotas. It is planned to expand this program, if funds are available, to include all tuberculin negative individuals.

The control of tuberculosis does not stop when the case finding survey and BCG vaccination is completed. There must be repeated examinations at frequent intervals to discover new sources of infection. Roentgenograms of the chest should be made of all individuals reaching adulthood and yearly thereafter, if at all possible.

Finally, there should be provision for adequate medical and sanatorium care for all active cases discovered. From a public health point of view, isolation is necessary if the spread of disease is to be prevented. In addition, proper treatment may arrest the disease if it is not too advanced and restore the individual as a functioning member of society. The Indian Medical Service now has 1,012 beds in hospitals and sanatoriums for tuberculosis patients. In addition, there are about 300 beds under contract in county and state hospitals. In view of the mortality and morbidity data previously presented, it is obvious that, with an Indian population of over 400,000, many more beds are needed. The

Federal Government should be urged to augment the program of tuberculosis control by appropriating sufficient funds for the adequate provision and maintenance of hospitals and medical care. The time and money spent in discovering active cases will largely go to waste if beds are not available for treatment of those with remediable disease and for isolation of the infectious patients. It is short-sighted to concentrate on case finding, if treatment is to be delayed because of a shortage of beds. Even if beds are not immediately available, attempts should be made to isolate and treat patients in the home or establish separate dwellings in the villages until such time as hospital facilities can be obtained.

The heavy toll of the Indian population taken by tuberculosis for years can be reduced and eventually controlled if our knowledge of its epidemiology and treatment is put into practice. Because the Indians constitute such a small population of the United States and are so easily reached, and because they respond so well to treatment, there is no reason why the ultimate control of tuberculosis is not feasible. The recent development of streptomycin and the use of BCG vaccine have added much to our armamentarium against the tubercle bacillus. However, this does not mean that we relax our efforts and need not deter us from making immediate and conscientious use of the fundamental control measures now available.

SUMMARY

1) The high incidence of tuberculosis is the most outstanding disease problem among the Indians of the United States. There is no evidence that tuberculosis existed among them in pre-Columbian times. The prevalence of the disease, as indicated by mortality and morbidity rates, and by x-ray surveys, has shown a gradual decrease throughout the years, however, recent mortality figures are over five times that of the general population, and x-ray surveys have shown an incidence of over 3 per cent pulmonary lesions characteristic of tuberculosis.

2) The course and character of tuberculosis among the Indians does not differ significantly from that among the whites. Indians appear to exhibit no peculiar racial susceptibility to tuberculosis, and immunological factors have little influence in the high prevalence of the disease among them.

3) Environmental changes coincident with the advent of the whites, and subsequent socio-economic conditions on the reservations, have been largely responsible for the high rate of tuberculosis among the Indians. Inadequate medical care and facilities, dependent upon funds from the Federal Government, have also played an important part.

CONCLUSION

Although significant strides have been made to control tuberculosis among Indians, the accomplishments to date have not been satisfactory. There must be improvement in the economic status, sanitation, and medical facilities before any real results can be realized. Active case finding surveys are to be encouraged, and provisions made for adequate isolation and treatment of those found to have active disease. It has been shown that BCG vaccine has decreased mortality and morbidity rates, and has a place in the control program. This does not obviate the need, however, for the conscientious application of the fundamental control measures now available, which have proven so successful among the white population. For it is evident that tuberculosis among Indians is just as amenable to the proper methods of control as it is among the whites.

RESUMEN

1) El mas destacado problema sanitario entre los indios de los Estados Unidos es la frecuencia de la tuberculosis. No hay pruebas de que esa enfermedad existiera antes de la llegada de Colón. La frecuencia de la enfermedad segun la señalan los índices de morbilidad y de mortalidad así como el catastro radiológico, ha mostrado tendencia a decrecer a través de los años, sin embargo, las cifras recientes aun son más de cinco veces mayores que las de la población general y la investigación en masa por los rayos X ha demostrado una incidencia de más de 3 por ciento de lesiones pulmonares características de tuberculosis.

2) La evolución y el carácter de la tuberculosis entre los indios de Norteamérica, no difiere significativamente de lo que se observa en los blancos. Los indios no ostentan susceptibilidad racial alguna peculiar ante la tuberculosis y los factores inmunobiológicos tienen pequeña influencia en la alta frecuencia de la enfermedad entre ellos.

3) Los cambios ambientales coincidentes con la llegada de los blancos y las subsecuentes condiciones socio-económicas de las reservaciones, son en gran parte los causantes del alto índice tuberculoso entre los indios. La atención medica inadecuada y comodidades que dependen de el uso de fondos del Gobierno Federal, también han desempeñado un papel importante en esto.

CONCLUSION

Aunque se han dado pasos significativos en el control de la tuberculosis entre los indios de Norteamérica, lo obtenido hasta ahora no es satisfactorio. Debe haber mejoría de la situación.

económica de la sanidad y de las facilidades de atención médica antes de que puedan observarse resultados tangibles. Hay que estimular la búsqueda de los casos de enfermedad activa, proveer a su aislamiento así como a su tratamiento. Se ha demostrado que el uso de la vacuna BCG ha hecho decrecer la morbilidad y la mortalidad y que tiene este medio un lugar en el proyecto de dominio de la enfermedad. Esto no descarta la necesidad de aplicar conscientemente las medidas fundamentales de control ahora asequibles que han demostrado su eficacia entre la población blanca. Porque es evidente que la tuberculosis entre los indios es susceptible de responder a los métodos de eradicación como lo es entre los blancos.

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JOSEPH C PLACAK, MD, FCCP.
 PRESIDENT
 American College of Chest Physicians
 1949-1950



Dr Joseph C Placak Installed as College President

Dr Joseph C Placak was installed as President of the American College of Chest Physicians at the Fifteenth Annual Meeting of the College held in Atlantic City, June 2-5, 1949

Dr Placak was born in Cleveland, Ohio on February 22, 1882. He was educated in the Cleveland Public Schools, Western Reserve University and the University of Prague, Austria. For several years he served as medical director of the municipal sanatorium for tuberculosis in Cleveland and as Head of the Division of Tuberculosis, Cleveland City Hospital, a post which he held until 1942. He also served as Director of the Department of Medicine at St. Johns Hospital. Dr Placak served in the first World War as a major in the Medical Corps of the United States Army. He was Chief of the Medical Service at the Evacuation Hospital and a member of the Third Army Disability Board, Coblenz, Germany. His principal hospital connections are Consulting Physician, Lake County Memorial Hospital and Consulting Physician, Doctors Hospital. He is President of the Anti-Tuberculosis League of Cleveland and Cuyahoga County.

Dr Placak is a Fellow of the American College of Chest Physicians, the American College of Physicians, the American Medical Association, and a member of the Board of Internists, the Cleveland Academy of Medicine, the Ohio State Medical Society, the National Tuberculosis Association, the American Trudeau Society, the Public Health Committee of the Cleveland Chamber of Commerce, and the Health Council of Cleveland, Ohio.

Annual Meeting, Board of Regents

The Board of Regents of the College convened at the Ambassador Hotel, Atlantic City, Thursday, June 2 at 2 00 p m and again on Sunday, June 5 at 5 00 p m Dr Paul A Turner, Louisville, Kentucky, Chairman of the Board, presided The following Regents, alternates and invited guests attended the meeting

Paul A Turner, M D, Louisville Kentucky, Chairman
Donato G Alarcon, M D, Mexico City, Mexico
Robert J Anderson, M D, Washington, D C (invited guest)
Russell S Anderson, M D, Erie, Pennsylvania (invited guest)
Carl C Aven, M D, Atlanta, Georgia (Chairman, Board of Governors)
Dean B Cole, M D, Richmond, Virginia
Martin H Collier, M D, Blackwood, New Jersey
M Jay Flipse, M D, Miami, Florida (alternate)
Carl H Gellenthien, M D, Valmora, New Mexico
E E Glenn, M D, Springfield, Missouri (alternate)
Edward A Greco, M D, Portland Maine
Edward W Hayes, M D, Monrovia, California
Charles M Hendricks, M D, El Paso, Texas
Robert B Homan, Jr, M D, El Paso, Texas
William A Hudson, M D, Detroit, Michigan
Minas Joannides, M D, Chicago, Illinois
Lopo de Carvalho, M D, Lisbon, Portugal
Edwin R Levine, M D, Chicago, Illinois (invited guest)
S U Marietta, M D Washington D C
Louis Mark, M D, Columbus, Ohio
Amadeo Vicente Mastellari, M D, Panama City, Panama
Gustav Maurer M D, Davos, Switzerland
Donald R McKay, M D Buffalo New York
Fred M F Meixner, M D, Peoria, Illinois (invited guest)
Jay Arthur Myers, M D, Minneapolis, Minnesota
Antonio Navarrete, M D, Havana, Cuba
James M Odell, M D, The Dalles, Oregon
William E Ogden, M D, Toronto, Canada
Richard H Overholt, M D, Brookline, Massachusetts
J Winthrop Peabody, M D, Washington, D C
Walter L Phillips, M D, Cape Town, South Africa (invited guest)
Joseph C Placak, M D, Cleveland, Ohio
James H Stygall, M D, Indianapolis, Indiana
William C Voorsanger, M D, San Francisco, Calif (invited guest)
Murray Kornfeld, Chicago, Illinois, Executive Secretary
Harriet E Lumm, Chicago, Illinois, Assistant Executive Secretary

After the signing of the College Register, the newly elected Regents, the Regents from other countries, the alternate Regents and invited guests were introduced Dr Donato G Alarcon, Regent for Mexico, reported on the Congress of the Union of Latin American Tuberculosis Societies held in Mexico City last January in which the College participated Dr Gustav Maurer, Regent for Central Europe, reported on the progress of the College program in the countries under his jurisdiction

The Treasurer of the College, Dr Minas Joannides, then presented his report which was moved for adoption by Dr Antonio Navarrete, seconded by Dr Louis Mark, and approved by the Board The Report of the Treasurer of the College was published in the July issue of the journal

Dr Charles M Hendricks, Chairman of the Committee on College By-Laws, presented the revisions in the By-Laws of the College and entered a motion that the Board approve the revised By-Laws The motion was seconded by Dr E W Hayes and the revised By-Laws were adopted

The revised By-Laws were subsequently presented before the administrative session of the College on Saturday, June 4, for the vote of the membership and were approved unanimously

Dr E W Hayes, Chairman of the Council on Undergraduate Medical Education reported on the success of the book entitled "The Fundamentals of Pulmonary Tuberculosis and Its Complications" which has recently been published under the sponsorship of the College Dr Hayes reported that the companion book on nontuberculous diseases of the chest is almost completed and will be published at an early date Dr Joseph C Placak declared that a vote of thanks should be given to Dr Hayes for his untiring efforts, the motion was seconded by Dr Donald R McKay, who stated that the New York Chapter of the College has presented a copy of "The Fundamentals of Pulmonary Tuberculosis and Its Complications" to the library of each of the New York State medical schools Dr Hayes' report was unanimously adopted

Dr J Winthrop Peabody, Chairman of the Council on Postgraduate Medical Education, presented his report of the activities of the council during the past year and the plans for the coming year It was announced that postgraduate courses in diseases of the chest will be given in Chicago, September 19-23, in Minneapolis, October 20-22, in New York City, November 14-18, and in San Francisco, December 5-9, with the cooperation of the College Chapters in the various states and the staffs of the leading medical schools and hospitals Dr Peabody's report was accepted with a vote of appreciation for his excellent work

In the absence of Dr Andrew L Banyai, Milwaukee, Wisconsin, Chairman of the Council on European Affairs, the report of this council was presented by Dr Joseph C Placak, the Vice-Chairman Dr Placak reported that an invitation was received from Dr A Omodei Zorini, Director of the Forlanini Institute, Rome, Italy, to hold the First International Congress on Diseases of the Chest in Rome in September of 1950 This Congress to be sponsored by the Council on International Affairs of the College After complete discussion by the members of the Council on International Affairs it was unanimously voted that proper arrangements be made for this Congress Those present and voting at the council meeting held on June 5 were

Professor Lopo de Carvalho
Professor Gustav Maurer
Dr Richard H Overholt
Dr Chevalier L Jackson
Dr Jay Arthur Myers

Dr Italo Volini
Dr Minas Joannides
Dr Edgar Mayer
Dr Joseph C Placak

The Council on International Affairs presented the following resolution

THEREFORE, BE IT RESOLVED, That the Board of Regents of the American College of Chest Physicians accept the recommendations of the Council on International Affairs and authorize the holding of the First International Congress on Diseases of the Chest in Rome, Italy, in the fall of 1950

Upon motion by Dr Louis Mark and seconded by Dr S U Marietta, the report of the Council on International Affairs was approved in its entirety

Dr Russell S Anderson, Chairman of the Council of Tuberculosis Hospitals, presented a progress report This council has conducted a number of preliminary meetings at which time matters concerning tuberculosis hospitals and sanatoria were discussed A full report of the council will

be published as soon as the program under way has been completed. The report presented by Dr. Anderson was moved for approval by Dr. William E. Hudson, seconded by Dr. S. U. Marietta, and unanimously adopted.

Dr. Robert J. Anderson, Chairman of the Council on Public Health, presented the following report of the meeting of the council held in Atlantic City on June 2:

Council on Public Health, Members Present

Dr. Robert J. Anderson, Washington, D. C., Chairman
Dr. Benjamin L. Brock, Downey, Illinois
Dr. Clifton Hall, Springfield, Illinois
Dr. Robert G. McCorkle, San Antonio, Texas
Dr. John M. Pierson, Columbia, South Carolina

***Committee on Chest Diseases in Penal and Mental Institutions, Members Present**

Dr. O. L. Bettag, Chicago, Illinois, Chairman
Dr. P. J. Sparer, Denver, Colorado

***Committee on Occupational Diseases of the Chest, Members Present**

Dr. C. Howard Marcy, Pittsburgh, Pennsylvania, Chairman
Dr. Frank R. Ferlino, New York, New York
Dr. Charles E. Lyght, Rahway, New Jersey
Dr. F. Kenneth Albrecht, Topeka, Kansas
Invited Guests
Dr. Ernest Teller, Chicago, Illinois
Dr. A. J. Steiner, St. Louis, Missouri

***These committees serve under the Council on Public Health**

A review of Dr. Paul A. Turner's report as chairman of the preceding council opened the meeting. This report contained references to case finding programs which became the first subject for discussion. Attention was given specifically to the "follow-up" aspects of mass surveys. The expressions of the several members present was to the effect that case-finding is not accomplished until a fairly definite working diagnosis is reached. Many mass x-ray programs do not result in diagnoses based on history, examination, or laboratory procedures including standard size x-ray films and routine bacteriological studies, as was evident from instances cited by several of the council members. Instances were also related where follow-up had been good and was reflected by statistics obtained from tuberculosis case registers. The discussion that followed was centered around the question, how to obtain such follow-up. To this problem, the educational efforts of the College can contribute much. The discussion resulted in the adoption of the following resolutions:

WHEREAS, mass surveys have demonstrated their value in the detection of chest lesions,

WHEREAS, the follow-up of all suspected cases has not always been adequately organized, and

WHEREAS, the maximum results from surveys cannot be achieved without more complete follow-up,

THEREFORE, BE IT RESOLVED that the American College of Chest Physicians recommend to the Section on Preventive and Industrial Medicine and Public Health of the American Medical Association, and the Tuberculosis Committees of the state and local medical societies that (1) they approve the principle and practice of arriving at a working diagnosis before the case-finding effort can be considered complete, (2) that this can most expeditiously be accomplished through the referral of the x-ray suspect cases to designated, organized chest clinics or centers whether temporarily or permanently established.

The Council on Public Health then moved that the College go on record advocating the establishment and improvement of local health services.

The Council on Public Health moved that the College stress the establishment of programs of routine x-ray for all hospital admissions. It has been shown to be a productive case-finding procedure and offers educational potentialities.

Drs Bettag and Sparer reported for the Committee on Chest Diseases in Penal and Mental Institutions. They related programs operating in certain areas and stressed the need for more study and action in this field.

Drs Marcy, Ferlaimo, Lyght and Albrecht reported for the Committee on Occupational Diseases of the Chest. They indicated that the approach to the problems would be largely one of education of industrial and chest physicians.

The Council on Public Health then adjourned.

Motion was made for acceptance of Dr Anderson's report by Dr Jay Arthur Myers, seconded by Dr J Winthrop Peabody and carried.

Dr William C Voorsanger, Chairman of the Council on Public Relations, presented the following report of the meeting of the council.

The Council on Public Relations met on Thursday, June 2nd at 5 00 p m at the Ambassador Hotel. This was the first meeting of the year. The Executive Secretary, Murray Kornfeld, presented a book of clippings from various medical journals throughout the country demonstrating that the College has received very good medical publicity during the year. The Council stressed the point that general publicity would be very valuable, particularly with the lay public, but pending the time when sufficient funds are available for this purpose the College publicity must be restricted to physicians and medical publications, except at conventions and meetings held during the year.

The Council was gratified that the general office, with limited facilities and a limited number of employees, developed the amount of publicity it did during the past year. It represented a very considerable effort.

The Council on Public Relations wishes to make a recommendation to the Board of Regents, namely that \$250.00 be set aside each year as a prize for the best paper on any subject pertaining to diseases of the chest. The competition should be open to any physician in the world. A committee should be appointed known as the Medical Prize Committee or some other appropriate name. All papers presented should be in the hands of this committee in sufficient time before the annual meeting so that selection of the best one can be made. This paper should then be given priority at the annual session and the winner of the prize should read his paper in person, if possible.

The Council feels that by continuing its cooperation with the central office much can be done to put the College in a favorable light throughout the world.

Motion for approval of the report was made by Dr Charles M Hendricks, seconded by Dr Louis Mark and carried.

Dr Charles M Hendricks, General Chairman of the Council on Research, reported on the activities of his council and presented the following motion.

This council requests the Board of Regents to authorize the incoming President of the College to appoint a committee of three members of the Research Council whose duty it will be to organize a legally-separate organization for raising funds for the purpose of carrying on research in diseases of the chest.

Dr Louis Mark moved for the adoption of this resolution, seconded by Dr Minas Joannides, and unanimously carried.

Dr Placak thereupon appointed the following committee: Dr Charles M Hendricks, Chairman, Dr Jay Arthur Myers, and Dr Minas Joannides.

Dr James H Stygall, Chairman of the Council of Tuberculosis Committees, presented a report of the activities of his council. The council recommended that the tuberculosis committees in the state medical

societies be requested to cooperate with the Council on Public Health of the College for the purpose of obtaining statistical information regarding admission of tuberculous patients in general hospitals Dr Minas Joannides moved that this recommendation be approved, seconded by Dr William E Hudson, and carried

Dr Edwin R Levine, Chairman of the Council on the Management and Treatment of Diseases of the Chest gave a progress report of his council which was referred back to committee for the purpose of adjusting several details That part of the report dealing with the establishment of a Committee on Physiologic Treatment of Chest Diseases was approved by the Board A full report of this council will be published at a later date

Dr Richard H Overholt requested that resolutions recommending approval of the Senate and House of Representatives bills regarding the use of living animals for scientific investigation be prepared and brought before the administrative session of the College for adoption The motion was approved by Dr James H Stygall, seconded by Dr Carl C Aven, and carried The President of the College appointed a committee comprising Dr S U Marietta and Dr M Jay Flipse to prepare the resolutions These resolutions were approved by the membership at the administrative session held on Saturday, June 4 and are as follows

WHEREAS, There has been introduced into the Senate and the House of Representatives of the United States Congress similar measures identified as S1703 and HR4349 "to provide that unclaimed animals lawfully impounded in the District of Columbia be made available for scientific purposes to educational scientific and governmental institutions licensed under this act," and

WHEREAS, The passage of these measures would eliminate cruelties to animals through proper preparation and painless experimentation by licensed individuals or institutions and

WHEREAS, The use of animals for such purposes would advance the teaching of medicine and assist in the development of new methods of treatment of human disease to the benefit of mankind,

NOW, THEREFORE, BE IT RESOLVED, By the American College of Chest Physicians duly assembled at its annual meeting in Atlantic City that Senate Bill S1703 and House of Representatives Bill HR4349 be hereby approved and recommended for passage by the bodies concerned, and

FURTHERMORE, BE IT RESOLVED, That copies of this resolution be spread upon the minutes of the American College of Chest Physicians and that copies be sent to each member of the Senate and House Committee for Health and Research and also to the President of the United States

WHEREAS, there has been introduced in the House of Representatives of the Congress of the United States a bill identified as HR857 "to prohibit experimentation on living dogs in the District of Columbia and provide penalties for violation thereof," and

WHEREAS, the passage of this bill would prevent scientific investigation of the cause and treatment of diseases in humans by the several colleges, medical schools and hospitals including those operated by the federal government in said district, and

WHEREAS, the passage of the bill would set a precedent which might eventually threaten the entire country with similar legislation to the great detriment of medical progress including the teaching of medicine and development of new remedies for the treatment of human disease,

THEREFORE, BE IT RESOLVED, by the American College of Chest Physicians duly assembled at its annual meeting at Atlantic City that this legislation HR857 be disapproved, and

FURTHERMORE, BE IT RESOLVED, that copies of this resolution be spread upon the minutes of the American College of Chest Physicians

and that copies be sent to each member of the Senate and House Committee for Health and Research and also to the President of the United States

Mr Murray Kornfeld read a letter received from Sir Sidney Sewell of Melbourne, Australia, Regent of the College, which was written shortly before his death Dr Paul A Turner proposed that all present stand for a minute of silence to the memory of the departed dear friend and colleague

Telegrams received from Dr Andrew L Banyai, Milwaukee, Wisconsin, Dr Harry C Warren, San Francisco, California, and Dr Hollis E Johnson, Nashville, Tennessee, expressing regret at not being able to attend the meeting because of illness in their families, were read and the Executive Secretary was authorized to send appropriate replies to each of these members of the Board of Regents

Dr Andrew L Banyai was elected by the Board of Regents to serve as a member of the Committee on Nominations

Dr James H Stygall was elected by the Board of Regents to the Executive Council

Dr William A Hudson was re-elected as Historian of the College

Dr Paul A Turner was re-elected Chairman of the Board of Regents Meeting adjourned

Scientific Exhibits, American Medical Association Section on Chest Diseases

The first Section on Chest Diseases in the Scientific Exhibits of the American Medical Association was presented at the Atlantic City meeting last month There were nine exhibits in the section, all of which attracted a great deal of interest The exhibit on "Tumors of the Lung—A Pathologic Study of Surgical Lesions" presented by Drs J R McDonald, L B Woolner and A H Bulbulian of the Mayo Clinic, Rochester, Minnesota, was awarded the Bronze Medal

First Section on Diseases of the Chest American Medical Association

The first meeting of the Section on Diseases of the Chest in the American Medical Association was held in Atlantic City on Wednesday, June 8 and Thursday, June 9 Registration at the meeting was 384, as reported by the American Medical Association, placing the Section on Diseases of the Chest in ninth place among the eighteen scientific sections

At the Executive Session held on Thursday, June 9, the following officers were elected

Walter E Vest, M D, Huntington, West Virginia, Chairman
Alvis E Greer, M D, Houston, Texas, Vice-Chairman
Jay Arthur Myers, M D, Minneapolis, Minnesota, Secretary
Hollis E Johnson, M D, Nashville, Tennessee, Delegate
Karl H Pfuetze, M D, Cannon Falls, Minnesota, Alternate

Dr S U Marietta, who served as chairman of the Section during the preceding year and Dr Jay Arthur Myers who served as Secretary are to be congratulated upon the splendid program arranged Dr Myers was re-elected to serve as Secretary of the Section for a three year term

College News Notes

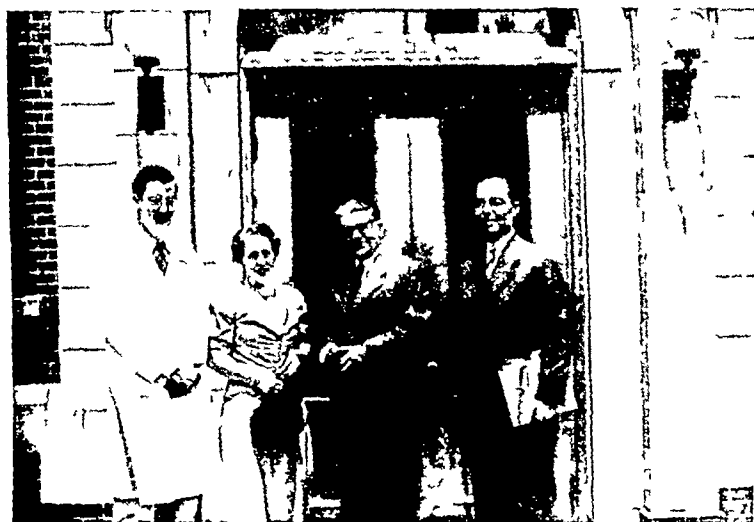
Dr Chevalier L Jackson was recently elected to the executive committee of the Philadelphia Laryngological Society

Dr Paul H Holinger, Chicago, Illinois, presented a paper on endoscopic cinematography at the Fourth International Congress of Otolaryngology held in London, England, July 17-24 From London, Dr Holinger went to Lisbon, Portugal to address a group of otolaryngologists Following this he will travel to South America where he will present papers and postgraduate courses in endoscopy in Buenos Aires and Santa Fe, Argentina, and Rio de Janeiro and Sao Paulo, Brazil

Dr Joseph Burrascano of New York City recently spoke before the New York University Institute of Rehabilitation on "The Diagnosis and Control of Tuberculosis "

Copies of the outline on "The Pneumoconioses" which Dr Oscar A Sander of Milwaukee, Wisconsin, presented at the round table discussion on "Dust Diseases" held at the annual meeting of the College in Atlantic City, are available for distribution to interested physicians Please write to the Executive Offices of the College, 500 North Dearborn Street, Chicago 10, Illinois, for copies

Professor Lopo de Carvalho Visits the United States



Professor Lopo de Carvalho (third from left) newly elected Regent of the College, of Lisbon, Portugal, his wife and Maderos Galvao, MD (right), Medical Director of the Vasconcellos Porto Sanatorium, Portugal visiting with Marcio Bueno, MD, Medical Director of the Fall River Tuberculosis Hospital, Fall River Massachusetts after attending the Annual Meeting of the American College of Chest Physicians in Atlantic City, June 2-5, 1949

Dr Evarts A Graham Receives College Award



Dr Graham was presented with the College Medal and Certificate of Award for meritorious achievement in the specialty of diseases of the chest at the annual meeting of the College in Atlantic City. The Award was made by Dr Jay Arthur Myers, Minneapolis, Minnesota, Chairman of the Committee on College Awards, at the Annual Presidents' Banquet held at the Ambassador Hotel on June 4. Dr Myers' introductory remarks appear on the opposite page.

Dr Evarts Ambrose Graham

On May 12, 1931, as chairman of the Committee on Award of the National Tuberculosis Association I had the honor of presenting the Trudeau Medal to the physician who was one of the world's finest students of tuberculosis. This was Allen K Krause of the Johns Hopkins University. Tonight it is my honor on behalf of the Committee on College Awards of the American College of Chest Physicians to present the 1949 College Medal and Certificate of Award to one of the world's most famous chest surgeons. He was born in Chicago on March 19, 1883. After attending public school and Lewis Institute of that city, he entered Princeton University and received the degree of Bachelor of Arts in 1904. Rush Medical College, Chicago, conferred upon him the degree of Doctor of Medicine in 1907. After completing an internship at Presbyterian Hospital, he spent four years as fellow and special student in pathology and chemistry at Rush Medical College and the University of Chicago. During a part of this time and until 1914 he was assistant in surgery at Rush Medical College.

Having become highly qualified, he was appointed to a professorship in surgery at Washington University School of Medicine and became surgeon-in-chief at Barnes Hospital and St. Louis Children's Hospital, St. Louis, Missouri, in 1919. Thus, he has served in these capacities for three decades.

During World War I he was major, Medical Corps, United States Army, with the Empyema Commission in 1918 and was later commanding officer, evacuation hospital, number 34, in France. As chairman of the Empyema Commission he observed that about one half of the soldiers who had developed acute empyema following influenzal pneumonia had died. It was well known by him that pneumonia causes a marked temporary reduction in vital lung capacity and he was convinced that open drainage had been established in many of these cases too soon, that is, before the empyema or the pleural abscess was well established and while the vital lung capacity was still markedly reduced. Opening the thorax at that time allowed air to equalize the pressure in the pleural cavity, which not only affected the diseased lung, but because of the unstable mediastinum in the absence of adhesions and induration there was considerable encroachment upon the contralateral lung often so much as to result in asphyxiation. Therefore, many soldiers were dying, not from empyema or pneumonia, but from too early surgical interference.

The Commission adopted the closed method often with only an aspirating needle until the empyema was definitely established and the pneumonia so under control that vital capacity was not markedly reduced. If further treatment was still necessary open drainage through rib resection was employed. Soon the mortality markedly decreased under this treatment, which has since resulted in the saving of large numbers of lives.

Already I perceive that you have identified the recipient of the Medal, Dr. Evarts Ambrose Graham. You will recall that he developed cautory pneumonectomy at a time when little was being done for cases of both unilateral and bilateral bronchiectasis whose disease had not been controlled and lobectomy was not considered wise or was impossible at that time. Many persons were definitely benefited by this procedure.

In 1933, Drs. Graham and Singer reported the case of a physician for whom they had removed the left lung for carcinoma of the bronchus.

This was the first case of total removal of a lung for carcinoma in a one-stage operation recorded in the world's literature. In due time this physician returned to his office and is still practicing medicine in Pittsburgh, Pennsylvania. This successful operation encouraged Dr. Graham and stimulated many others to consider similar surgery. Progress has been so rapid that today such procedures as lobectomy, pneumonectomy and segmental resections in many parts of the world are restoring invalids not only with cancer, but also with bronchiectasis and other conditions to good health and are saving the lives of many. The pioneer work in surgery of the chest of Dr. Graham and the fine techniques he subsequently developed are responsible in no small way, not only for the rapid advances in chest surgery, but also for the skill with which operations are performed.

Dr. Graham has always had the courage of his convictions. For example, when wild enthusiasm was being manifested for x-ray and radium therapy for pulmonary malignancy, he openly condemned the procedure as never having resulted in a cure for cancer. Again, when bronchoscopists and others were advocating the removal of bronchogenic carcinoma by bronchoscopic methods, Dr. Graham pointed out the utter impossibility of removing all malignant tissue in this manner. He strongly recommended lobectomy or pneumonectomy in order that the entire cancer might be extricated with certainty. He stoutly maintained that every benign bronchial adenoma should be treated by drastic surgery rather than bronchoscopy since a considerable percentage may become malignant.

Dr. Graham holds membership in a large number of medical and scientific organizations in various nations. He has been president of the American Surgical Association, the American College of Surgeons and the American Association for Thoracic Surgery. He has contributed numerous articles to the medical and surgical literature, as well as books. He was co-editor of *Archives of Surgery* from 1920 to 1946, and of the *Annals of Surgery* since 1934. Since 1925 Dr. Graham has edited the *Year Book of Surgery*. Here he has brought together annually in one volume, the outstanding contributions of the world in surgery. This has been a fine service to surgeons everywhere. Since 1931 he has been editor of the *American Journal of Thoracic Surgery*. He and his associate editors have selected a fine array of articles for publication which have dealt with practically every phase of chest surgery and closely allied subjects.

He has been in great demand on committees, boards, etc. In 1922 he was sent by Rockefeller Foundation to Great Britain to investigate teaching of surgery in British medical schools. From 1925-39 he was a member of the Medical Fellowship Board, National Research Council, from 1937-41 chairman, American Board of Surgery, and 1940-46 chairman, Committee on Surgery, National Research Council. For nine years he served as a member of the National Board of Medical Examiners.

Six fine universities in the United States and Canada have conferred upon him the degree of Doctor of Science, and others the degree of Doctor of Law. He has been called to give special lectures to all parts of the United States and to Australia and England. Obviously the accomplishments of this man and his recognition around the world classifies him as one of the truly great world citizens of all time.

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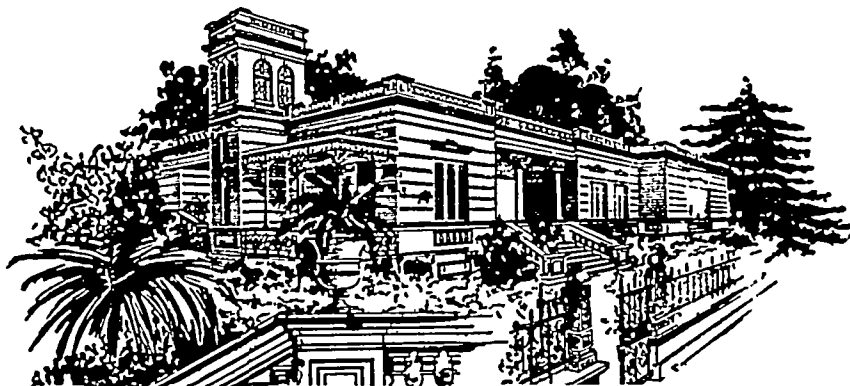
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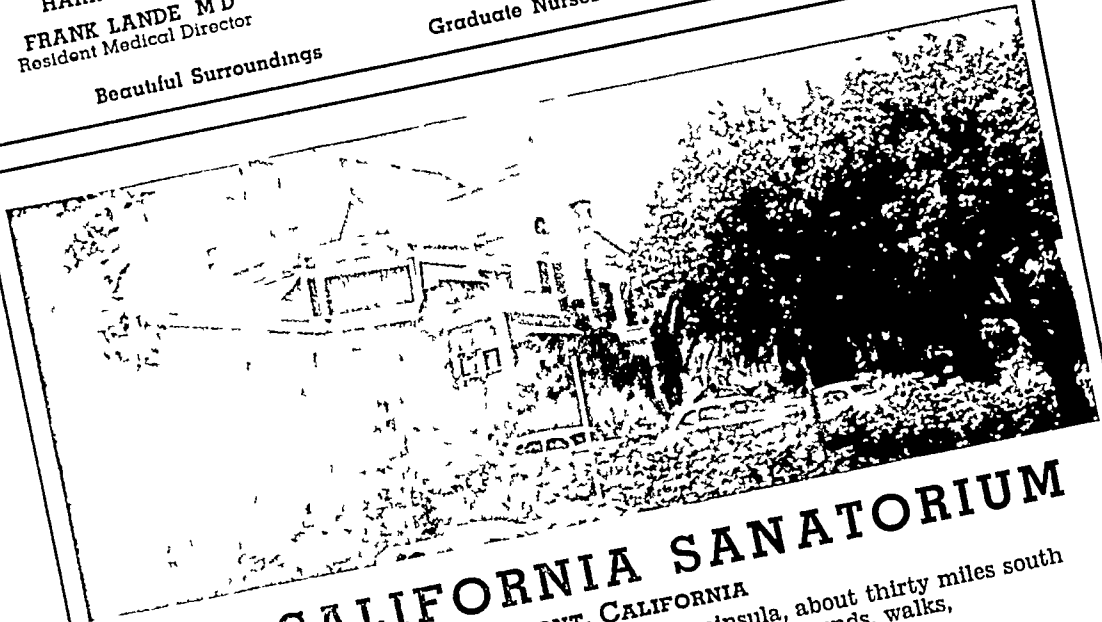
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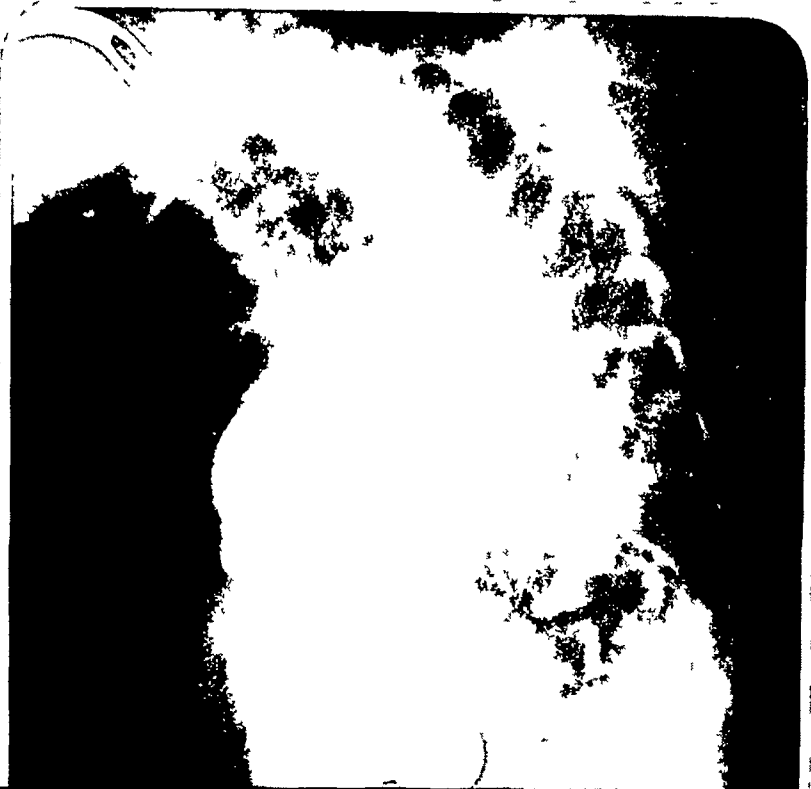
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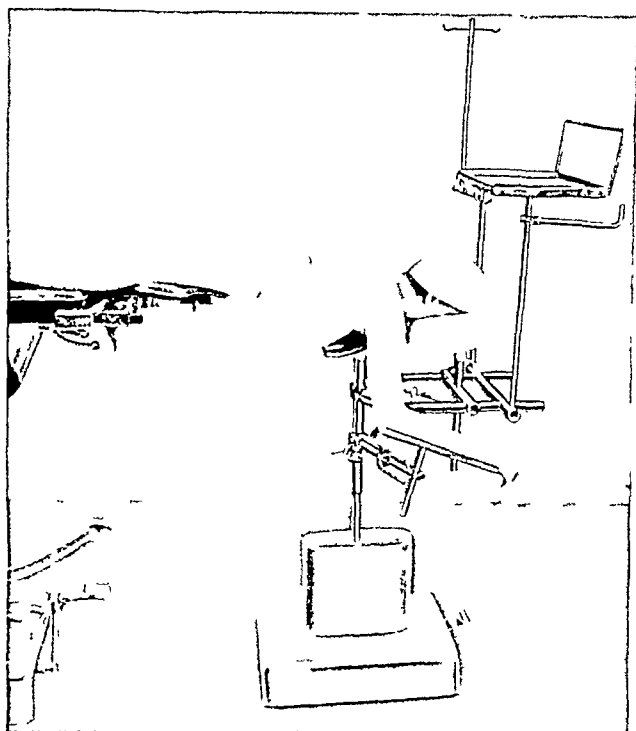
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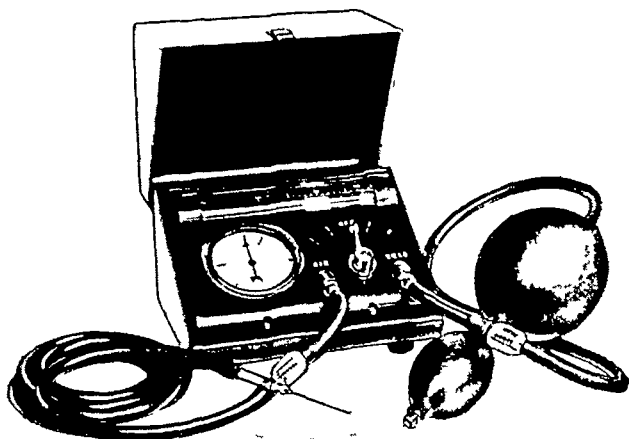
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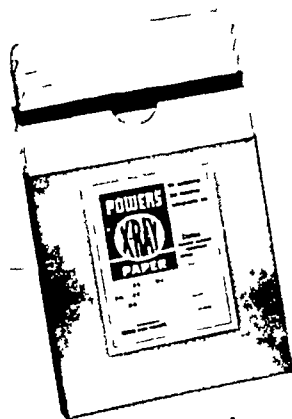
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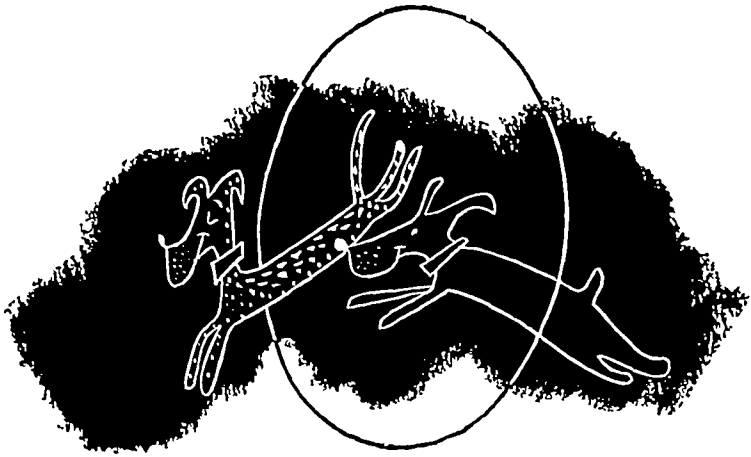
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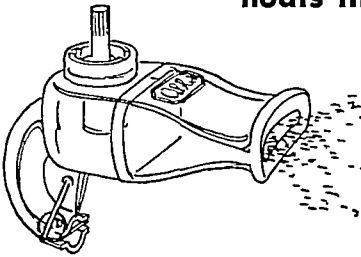
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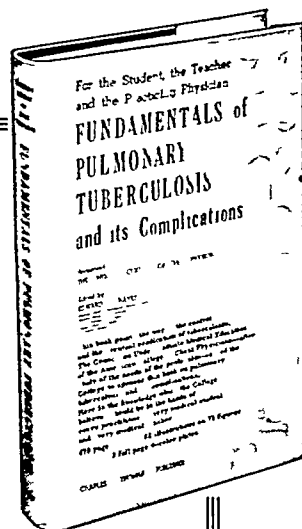
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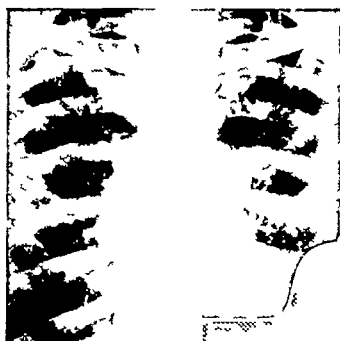
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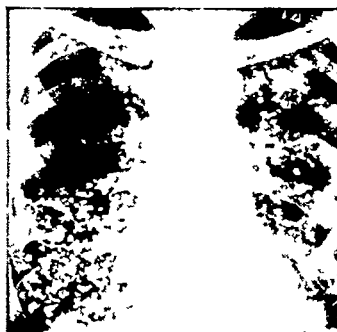
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Bronchiectasis and Its Management A Report of 277 Cases

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Bronchiectasis is a common disease about which there is little unanimity of opinion as to the best form of treatment. While the development of pulmonary resection by improved thoracic surgical methods has permitted the radical cure of many cases, the common use of penicillin and other antibiotics has allowed a considerable vogue for medical and more conservative measures in handling other patients with this disease. This study was undertaken not to advocate any type of therapy over all others but rather to evaluate a fairly large group of patients treated by many methods and observed by one individual over a long period of time, and to describe the present policy in handling cases of bronchiectasis which has evolved from this experience.

The study includes 277 personally observed patients admitted to the Lahey Clinic between the years 1936 to July 1948. Since in the study and treatment of these patients there has been close cooperation between internist, roentgenologist, surgeon, otolaryngologist and bronchoscopist this has, in fact, been a group experience. Adams and Ficarra¹ have already reported on an appraisal of the surgical treatment of bronchiectasis in 50 cases which includes some of the patients in the present series. Since many persons are not candidates for surgery for one reason or another, the present group is larger and unselected except that there were a few additional patients whose records were not available for review.

The sexes (Table 1) are evenly divided and the ages range from 4 to 80 years. Age distribution (Chart 1) shows a remarkable uniformity throughout all decades up to age 50 except for the

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children who are in the minority among general clinic admissions There are a surprising number of patients in the older group above 50

The presenting complaint of patients on admission is shown in Table 2 The most frequent complaint was cough, occurring in 136 or almost half of the series It is of interest that 33 came in chiefly because of hemoptysis Most patients who come to the clinic because of this symptom eventually prove to have bronchiectasis Weakness, fatigue and malaise not uncommonly are the predominant symptoms and in all such persons, as well as those with unexplained fever, bronchiectasis must be considered Often the chief complaint was obviously unrelated to the pulmonary condition which at times was of secondary importance and therefore received no particular diagnostic or therapeutic attention because the primary disease took precedence

TABLE 1
Bronchiectasis 1936-1948

Number of cases	277
Male	135
Female	142
Youngest	4
Oldest	80

BRONCHIECTASIS AGE DISTRIBUTION

ALL CASES ☐ SURGICAL CASES ☒

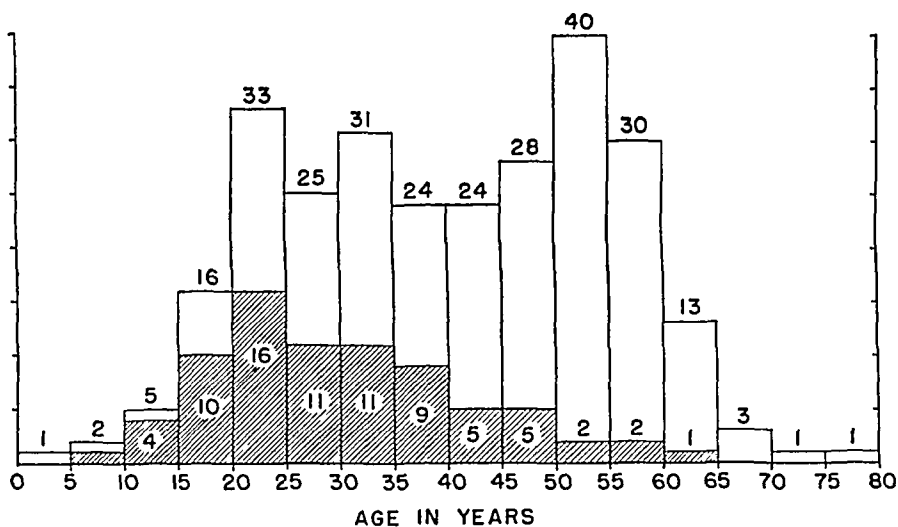


CHART 1

The chief symptoms of bronchiectasis are cough, sputum, hemoptysis, dyspnea and chest pain Table 3 shows the number of times each of these occurred Although almost all patients had cough, in 10 instances this complaint could not be elicited Similarly, all but 23 patients had sputum No attempt was made to record type or amount of sputum It is our experience that sputum, though usually purulent, may be of any type, any amount from a teaspoonful to a pint or more daily and may even be intermittent, disappearing entirely for a period of time

It is important to note that over half the patients had hemoptysis at some time during the course of the disease and there is no doubt that practically all patients with bronchiectasis expectorate blood some time during their lifetime The amount of blood may vary from a tiny streak to a large exsanguinating hemorrhage By far the commonest experience, however, is for the patient to raise a few mouthfuls of blood at infrequent and irregular intervals with long periods of freedom from this symptom Hemoptysis occurred as the only symptom of any type in one case and without any other type of sputum eight times This is characteristic of the so-called dry bronchiectasis in which infection is minimal or absent although the bronchi are dilated Bronchiectasis, once productive of pus and mucus, may in the course of time

TABLE 2
Chief Complaint

Cough	136
Hemoptysis	33
Chest pain	11
Dyspnea	8
Asthma	8
Frequent colds	8
Malaise or fatigue	8
Sputum	4
Weakness	4
All other	57

TABLE 3
Five Major Symptoms

	Times Occurred	Times Chief Complaint
Cough	267	136
Sputum	254	4
Hemoptysis	154	33
Dyspnea	149	8
Chest pain	113	11
Patients with all symptoms	45	

"improve" to this dry condition Cough and hemoptysis occurred together as the only symptoms in 2 cases

Three patients had cough only, without pain, sputum, hemoptysis or other complaint Forty-five had all five of the major symptoms listed above Dyspnea and pain both occurred often enough to be considered a common part of the symptomatology One patient had no symptom that could be attributed to the bronchiectasis She entered for a stricture of the bladder neck and was found to have persistent basal rales on physical examination and typical roentgenologic evidence of bronchiectasis

Most of the patients (Table 4) had physical signs in the chest although these were often minimal, such as transient basal rhonchi or slight suppression of breath sounds over the affected lobe Many times these physical signs were elicited only by repeated examinations Probably of much more importance is the fact that 29 patients had absolutely no physical signs in the chest at any time by any observer Even extensive bronchiectasis can exist without causing detectable physical signs

Clubbing of the terminal phalanges which has long been considered a classical sign of bronchiectasis was not as frequent as might be expected, occurring only 53 times, often minimal in degree Its presence should always lead to consideration of the possibility of bronchiectasis but its absence obviously has no value in ruling out the disease

The pathogenesis of bronchiectasis in these cases was seldom clear cut The onset was often insidious and early in life so that the patient had little recollection of the events leading up to the first symptoms On the other hand, there were times when the disease seemed definitely to follow pneumonia or other respiratory infection, whooping cough, aspiration of a foreign body, and so forth One patient's cough began immediately after he was rescued from drowning and seemed definitely related to aspiration or other consequence of this near tragedy One seemed related to the partial bronchial obstruction caused by a large intrathoracic goiter One patient's symptoms began after an attack of diphtheria requiring a tracheotomy Three patients gave a history of inhaling mustard gas during World War I These men usually gave a history of cough which had been considered to be tuber-

TABLE 4
Physical Signs

Pulmonary	243
Clubbed fingers	53
No physical signs	29

culous and was treated as such. Finally, bronchograms confirmed the diagnosis of bronchiectasis. The two cases of foreign body will be mentioned later.

Recent studies² have confirmed the opinion that bronchial obstruction and infection are two of the most important factors in the etiology of bronchiectasis, so situations which might cause either of these were considered of possible historical interest. Table 5 shows the number of times these factors were found. The high incidence of pneumonia and pleurisy is striking. It is impossible to determine in most cases no matter how carefully the patient is questioned whether pneumonia caused the bronchiectasis or occurred because the patient had bronchiectasis. It has frequently been observed that patients who have bronchiectasis are extremely susceptible to pneumonia or pneumonitis and sometimes have such complications almost annually. In fact, the history of frequent attacks of pneumonia should in itself lead to a strong suspicion of bronchiectasis. The charts examined undoubtedly record whooping cough much less frequently than its actual incidence and probably this disease is frequently the inciting cause of bronchiectasis beginning in childhood.

Although most asthmatics do not have bronchiectasis, some patients with asthma of long standing develop the cylindrical type as a result and it is inevitable with the high percentage of allergic individuals in this country that mere coincidence would account

TABLE 5
Etiologic Factors

Pneumonia	159
Pleurisy	106
Asthma	20
Whooping cough	15
Tuberculosis	13
Post-tonsillectomy	5
Empyema	5
"Flu"	4
Mustard gas	3
Measles	3
Postoperative pneumonia	3
Foreign body	2
Emphysema	2
Situs inversus	2
Tooth extraction	1
Pulmonary abscess	1
Trauma	1
Tracheotomy	1
Large goiter	1
Near drowning	1

for both asthma and bronchiectasis being present in some patients Table 6 shows that 52 of our patients had allergic manifestations personally and 48 had family histories of allergy This is probably not more than the number to be expected by pure coincidence However, the importance of this observation lies in the fact that treating the allergy is often an important part of the therapy and in some cases may make the difference between success and failure

All patients in this study had roentgenograms of the chest at least once These were either single or stereoscopic postero-anterior projections, often with special positions and technics to augment the study Plain roentgenograms before the instillation of iodized oil were considered abnormal in a high percentage of cases Two hundred and fifty-one were abnormal in some respect and usually the proper diagnosis was at least suggested by the roentgenologist (Table 7) In our experience, bronchiectasis can be diagnosed accurately from such studies in most cases and bronchography with iodized oil serves as a means of confirming the diagnosis and, more important, is the only method by which its extent and segmental distribution can be accurately mapped Again of importance are the patients who showed no evidence of disease even on careful roentgenologic study In 26 cases there was nothing abnormal on the roentgenogram even after the diagnosis had been proved and the films were reviewed Therefore, the finding of a completely normal roentgenogram cannot be considered to rule out bronchiectasis when there is reason to suspect it

Lipiodol bronchograms were made on 196 patients, sometimes more than once These were always abnormal, the diagnosis of

TABLE 6

Allergy and Bronchiectasis 277 Cases

Patient allergic, family nonallergic	29
Patient allergic, family allergic	23
Patient nonallergic, family allergic	25
Patient nonallergic, family nonallergic	200

TABLE 7

Diagnostic Studies 277 Cases

X-rays abnormal	251
X-rays normal	20
X-rays questionable	6
Bronchograms	196
Bronchoscopies	101
X-rays only	70
X-ray and bronchogram (no bronchoscopy)	99
X-ray and bronchoscopy (no bronchogram)	8
Neither x-ray nor physical signs	9

course not being made unless dilated bronchi were visualized. In 101 cases, bronchoscopy was performed. Usually this examination was followed by bronchography, but in 8 cases iodized oil was not used, the information obtained from bronchoscopy alone being considered adequate for the purpose. In 71 cases the plain roentgenogram was considered sufficient for diagnosis without further study. Ninety-nine patients had bronchography but not bronchoscopy.

Bronchography is considered a necessary procedure prior to pulmonary resection and it has become our practice, evolved through experience gathered from the patients herein reported, to insist that all five pulmonary lobes be visualized prior to operation so that an accurate base line is obtained from which to judge how much surgery to advise and to evaluate postoperative results and complications. In three cases early in the series, bronchograms were not done before surgery although bronchoscopy had been performed. On the other hand, we usually have no qualms about advising surgery without bronchoscopy provided bronchograms have been successful and no lobe or segment is obstructed. Roentgenologic evidence of tumor or atelectasis, nonfilling bronchi to a lobe on the bronchographic study, and the clinical finding of wheeze are considered urgent indications for preoperative bronchoscopy, but often, it is done in patients without these findings. Operations were performed on 32 patients who had bronchograms but no preoperative bronchoscopy.

One patient had neither bronchoscopy nor bronchogram and deserves special mention. This man of 34, entered because of asthma and was found on routine roentgenography to have a rounded mass in the left upper lobe which appeared to be a tumor (Fig. 1). A left upper lobectomy was performed and the mass pathologically was found to be not a tumor but a single large bronchiectatic cavity with squamous metaplasia of the lining epithelium. His subsequent course was uneventful although his asthma was an unrelated problem.

An interesting and important small group of patients is that in which there were neither abnormal physical nor roentgenologic signs. In these cases the symptoms were suggestive enough to lead to bronchography in spite of the otherwise negative findings and bronchiectasis was proved.

Many patients did not require bronchography or bronchoscopy because the diagnosis could be made with accuracy by the simpler methods and because it was apparent that surgery could not be offered because of age, extent of disease or generally poor condition. It was not necessary in these cases to delineate the segmental distribution of the disease to institute treatment. Some came for

confirmation of advice given elsewhere, or refused further study or had another condition which was more important than the bronchiectasis. In these cases bronchograms and bronchoscopies were usually omitted.

The lower lobes were involved much more frequently than the others, the middle lobe and lingular segment of the left upper lobe somewhat less frequently and the upper lobes least often (Table 8). The total number of left lobes (295) was almost exactly equal to the number of right lobes (292). A single lobe was involved exactly 100 times (Table 9), two lobes 86 times, three lobes 50 times, four lobes 21 times, five lobes twice and six lobes six times. For practical surgical reasons the lingula has been listed here as a separate lobe although anatomically it is a dependent portion of the lower anterior part of the left upper lobe. In 121 cases the disease was bilateral, in two the entire right lung was involved with normal left lung and in 9 the entire left lung was diseased while the right remained normal.

An effort has been made to determine whether the lower lobes are usually involved alone or in conjunction with the adjacent middle lobe and lingular segment. In the cases in which bronchograms were done, when the right lower lobe was involved, the



FIGURE 1 Bronchiectatic cavity in left upper lobe with squamous metaplasia of epithelium appearing to be a tumor

middle lobe was also diseased in 65 cases but in 40 cases it was normal. On the left side the lingula was involved with the lower lobe 63 times and uninvolved 78 times. In addition, it could be determined that when the apical portion of the left upper lobe was diseased the lingula was similarly diseased 18 times and was uninvolved only six times.

Thirteen patients gave a history of having had tuberculosis. This could not always be confirmed. Some of these patients had no clinical or roentgenologic signs of tuberculosis, either healed or otherwise, and had sputa repeatedly negative for acid fast organisms. On the other hand, several patients were discovered to have previously undetected roentgenologic evidence of old healed lesions. In all, 24 cases were found in which tuberculosis was present, usually as a healed scar of obsolescent disease but at times definitely of etiologic importance in producing the bronchiectasis. One patient had tuberculosis of the spine and an unrelated nonspecific bronchiectasis. One other is of special interest. This patient, a young woman of 19, entered the clinic in 1945 complaining of cough of many years' duration. As a child she had spent a total of almost two years in a tuberculosis sanatorium because of her symptoms but all studies had been negative and she was finally discharged as nontuberculous. Our roentgenograms, bronchoscopy and bronchography established the diagnosis of bilateral bronchiectasis and as the first stage of a contemplated

TABLE 8
Lobes Involved

Right upper	25	} 292
Right middle	103	
Right lower	164	
Left upper	26	} 295
Lingula	75	
Left lower	194	

TABLE 9
Number of Lobes Involved

One	100	
Any two	86	
Any three	50	
Any four	21	
Any five	2	
All six	6	
Unilateral disease		145
Bilateral disease		121

bilateral surgical procedure, a right middle lobectomy was done. Recovery was uneventful but when she returned for study prior to the second operation her sputum was found to contain tubercle bacilli. Roentgenograms (Fig 2) showed an infiltrative lesion at the apexes which at first was thought to be retained lipiodol but which further study indicated was increasing in amount. Guinea pig inoculation of the sputum confirmed the tuberculous nature of the disease, cavitation in the left (unoperated) lung developed and in spite of streptomycin and sanatorium care, she went rapidly down hill to death within a few months after the tuberculosis was first diagnosed. Since as far as could be determined there had been no recent exposure to the disease, it was conjectured that she probably had a small healed tuberculous focus in the lung which was lighted up by the surgical procedure. Such a latent focus presumably could have been acquired during her long sojourn in a sanatorium as a child. Although this unhappy outcome seemed unavoidable, it points out a danger which should always



FIGURE 2 Bronchogram after right middle lobectomy showing bronchiectasis in both lower lobes. Note exudative tuberculosis in both apexes and first and second right interspaces

be considered before surgical extirpation of a portion of a lung which has ever been involved by tuberculosis

A bacteriologic study of the sputum revealed a great variety of infecting organisms. Ninety-three patients had such studies. Rarely was only one type of organism isolated and multiple cultures on the same patient frequently revealed different bacteria. Twenty-nine species of bacteria and five fungi were identified. There was no reason to associate any particular microorganism or any combination of such with any type or severity of disease. On the other hand, the appearance, color, quantity and odor of sputum may be an indication of its bacteriologic content. Several types of gram negative rods were found. These have assumed new importance since the use of streptomycin has become practical for they usually are penicillin-resistant but can be inhibited by streptomycin, at least to some degree. Sputum originally containing gram positive organisms may, after the administration of penicillin for several days, contain none or few of these and repeat examination will show almost pure cultures of gram negative (penicillin-resistant) forms. Failure of penicillin to reduce significantly the amount or quantity of sputum is usually a good indication that gram negative or other penicillin-resistant bacteria predominate. The addition of streptomycin in these cases may be gratifying.

We have seen one patient in whom prior to operation thorough administration of penicillin resulted first in a sterile sputum, then in complete absence of any sputum, a fortunate condition which persists to the present time even though a still bronchiectatic right lower lobe remains after resection of a severely diseased left lower lobe and lingula. In most cases, antibiotics can produce temporary amelioration of symptoms with a decrease in amount of sputum which usually also becomes thinner and lighter in color and less malodorous. Unfortunately, however, respiratory infections sooner or later ensue with a flare-up of sputum sometimes amounting to pretreatment measurements. Many such relapses can be treated again with antibiotics. Sulfadiazine, sulfamerazine or any of the associated drugs similarly may produce some temporary benefit. We have never seen a case in which well established bronchographically proved dilatation disappeared on any form of medical therapy although some questionable cases have become definitely normal as far as can be determined without pathologic examination.

Penicillin has been used on 81 in this group and streptomycin on 13 patients. All getting the latter drug also had the former.

In the treatment of these cases of bronchiectasis many methods have been used, not only by us but sometimes by others before

the patients came under our care. Certain of these would be of historical interest only for many measures used at one time have since been abandoned as better ways of handling the problem have been developed. It is our opinion now that only surgical removal of the diseased area can produce a cure. Medical measures, useful as they are, will always fall short of that goal. Therefore, when planning the therapy of these patients we try if at all possible to bring them to surgery. Patients with more than minimal disease or minimal symptoms are advised to have operations unless there is some contraindication. Among these are included old age, poor general condition which would make a surgical procedure unusually hazardous, some severe associated disease such as valvular or coronary heart disease, severe hypertension, nephritis, pulmonary emphysema and so forth, or a disease which in itself takes precedence over the treatment of bronchiectasis, such as psychosis, malignant disease anywhere in the body, brain abscess, severe asthma, active tuberculosis, and so forth. Another contraindication to surgery is disease so widely scattered and severe that its removal would leave insufficient lung tissue to support life. Age in itself is difficult to classify as a contraindication. With increasing experience, the improved skill of surgeons and anesthesiologists and the use of antibiotics and wholesale blood transfusions, it has been possible in recent years to operate successfully on patients who formerly would have been denied this boon. The age which is considered a contraindication has steadily increased through the years until now we occasionally operate upon patients in their fifties who are otherwise well, and have sent one patient to surgery at the age of 60, with a successful outcome. One patient, aged 63, was operated on transthoracically for diaphragmatic hernia without ill effect and without disturbing the minimal bronchiectasis of the lower lobe. The youngest patient to have lobectomy was seven years old. Chart 1 indicates a rather smooth distribution curve of ages at operation, with the peak lying between 21 and 25 years.

Seventy-eight patients have had 95 operations, removing 126 lobes or segments of lobes. Table 10 indicates the number of times each operation has been performed. Thoracoplasty has been necessary either to close an empyema cavity or a bronchial fistula six times and thoracotomy to drain empyema five times.

In the entire series of cases bronchiectasis has been unilateral 145 times and bilateral 121 times, the remaining cases being questionable. Of the 121 patients with bilateral disease, 25 have been subjected to surgical resection and six of the 25 have had lobectomy or bilobectomy on both sides. In the other 19 bilateral cases surgery on the worse side has allowed so much improvement

that the second operation was deemed unnecessary or some contraindication has arisen

Disease of the paranasal sinuses plays an important part in the management of bronchiectasis. Conjecture as to whether the sinusitis or the bronchiectasis is the first offender is usually fruitless and always useless. More important is the frequency with which the two diseases are associated and the method of handling the sinus disease when present in conjunction with bronchiectasis. In this series of cases definite sinusitis was proved to be present in 93 persons. Sixty-nine had suppuration while in 24 the membranes were hyperplastic but no pus was present. Undoubtedly, the actual number of patients with diseased sinuses should be higher, this portion of the examination being neglected sometimes for a variety of reasons. Thirty-five patients had radical sinus surgery. The great majority of these had suppurative disease. Several others were advised to have sinus surgery but have either refused or postponed the procedure. Many of the patients not subjected to operations had multiple irrigations or other measures of treatment which produced satisfactory results.

Along with these surgical procedures so-called medical measures of treatment were used, and for the patients in whom surgery was possible, constituted the only form of therapy. General hygienic measures are important. Considerable improvement at times takes place simply by correcting hours of rest, dietary habits and stressing the avoidance of fatigue, respiratory infections, excess tobacco or alcohol. Patients are encouraged to get a long night of rest in bed, daily naps if possible or, in extreme cases, even

TABLE 10

Operations 78 Patients

Right upper lobectomy	1
Right middle lobectomy	8
Right lower lobectomy	9
Left upper lobectomy	7
Lingulectomy	1
Left lower lobectomy	23
Right upper and middle lobectomy	1
Right middle and lower lobectomy	5
Left lower and lingulectomy	21
Right pneumonectomy	1
Left pneumonectomy	4
Drainage of empyema	5
Thoracoplasty	6
Multiple segmental removal	2
Right lower and lingulectomy (situs inversus)	1
TOTAL	95

complete bed rest for varying periods of time. High protein diets with or without protein supplements often seem to be beneficial, particularly in those with large amounts of purulent sputum. Although no studies of serum protein have been made, it is not at all unlikely that these people lose large amounts of protein in their copious sputum. Vitamin supplements are given for the same reason usually in the form of one of the commercial polyvitamin capsules two or three times daily. Smoking is usually forbidden not because tobacco is of etiologic importance but because inflamed bronchi from any cause are irritated by smoke, with an increase in cough. In fact, several patients with proved bronchiectasis have stopped coughing entirely when smoking was abandoned.

Unless there has been recent severe hemorrhage, severe hypertension, dyspnea or some other contraindication, all patients are encouraged to perform postural drainage faithfully. They are instructed in the proper method as soon as the diagnosis is made and are started on four drainages of 10 minutes daily. If expectoration still occurs between these drainages, the number per day is increased and when the sputum becomes scant or drainages become nonproductive, the number may be reduced. However, all are encouraged to continue this procedure at least once a day. This method of draining purulent secretions is nearly always followed by a decrease in cough and improvement in feeling of well-being which bespeaks its value.

To facilitate the raising of secretions, some form of expectorant is usually prescribed, the one most frequently used being potassium iodide in doses of 10 drops of the saturated solution in water by mouth three times daily. It is a distinct clinical impression that this drug has a mildly antiseptic effect and causes definite thinning of bronchial mucus which in turn seems to soothe inflamed membranes, facilitate expectoration or at times paradoxically to reduce the amount of sputum. The latter phenomenon is perhaps explained by the fact that thinner mucus permits more nearly normal ciliary action in the bronchial mucosa, with resulting less need to expel secretions by cough.

In addition to the above general therapeutic measures two other classes of treatment may be important. These are the antibacterial and antiallergic. One by one as they have been developed and brought out for clinical use, the antibacterial drugs have been tried in bronchiectasis with varying success depending on the drug, the method administered, the bacteria present and the anatomical variations of the disease. There is still a place in certain cases for the sulfonamide drugs given by mouth and nearly all patients with bronchiectasis should have penicillin.

unless they have drug sensitivity, and some may be benefited by the addition of streptomycin

Penicillin is usually given both intramuscularly and by inhalation to hospitalized patients and by inhalation or orally to ambulatory patients To be effective when inhaled, the drug must be given two to five or more times a day Solutions containing 25,000 to 50,000 units per cubic centimeter are used and each dose is 1 cc For ambulatory patients who are working, more frequent inhalations are impractical and perhaps this suboptimal dosage explains the fact that in many patients the aerosols seem less effective than injected penicillin Recently, finely divided crystalline penicillin has been used as an inhalant, the so-called penicillin "dust" or "smoke"³ This promises to be a reasonably satisfactory method

Streptomycin is best given by intramuscular injection, combined if desired with inhalations of nebulized solutions One half gram four times a day is average dosage for injection and one half gram in divided doses as an aerosol The use of this drug is usually reserved for patients who do not respond to penicillin and it is customary to institute treatment with the latter drug If results are not good the sputum is cultured and if organisms that can be expected to respond to streptomycin are found, this agent is added

Both these antibiotics can be used in several ways Commonest is to give an initial thorough course of from one to two weeks, then to stop but to resume its use immediately if there is a respiratory infection or any relapse in the amount and purulent nature of the sputum An alternative method is to use the aerosol once or twice a day as maintenance therapy

The usual result after the administration of these drugs is that sputum decreases to a fraction of its former amount, loses any unpleasant odor it may have possessed and becomes lighter in color and clearer, in other words, more mucoid and less purulent

Both penicillin and streptomycin may be used for preoperative preparation and at times sulfadiazine is added Four to seven days of antibiotic therapy preoperatively are usually amply rewarded by a marked decrease in postoperative morbidity and complications so that total hospitalization is actually less than if the preoperative treatment is omitted

At times it has been necessary to discontinue penicillin aerosol because of the development of inflammation of the buccal mucosa and tongue, while an occasional patient develops urticaria or other forms of dermatitis from intramuscular penicillin The use of one of the antihistamine drugs may permit continuing the antibiotic even in the presence of this allergy However, we recently had

one patient being prepared for surgery who developed such a severe pruritic generalized vesicular eruption that penicillin had to be permanently abandoned. He was successfully carried through his operation and the postoperative period on streptomycin alone and developed no pleural infection.

Allergic individuals usually react excessively to infection and are prone to have severe and stubborn symptoms when afflicted by bronchiectasis or sinusitis. More than once symptoms have been seen to persist in a patient otherwise thoroughly treated until a full allergy regimen is instituted. Therefore, signs or hints of allergy should be carefully sought in all bronchiectatic patients, but particularly in those doing poorly. The history may show strong allergic tendencies in patient or family or he may have such signs as urticaria, atopic dermatoses, hay fever, wheezing, pale boggy nasal mucous membranes, hyperplastic sinusitis, and so forth. Clinical evaluation, including intradermal tests, may indicate elimination regimens or hyposensitization therapy which will make the difference between success and failure. Patients with severe asthma and mild bronchiectasis may do well on anti-allergic measures alone without the necessity for antibiotic drugs or surgery. Vaccines, either autogenous or of the common respiratory organisms, are likely to cause improvement, particularly in the patient with an allergic background.

Finally should be mentioned the beneficial effect of change of climate on certain persons. Cold, damp and changeable climates are conducive to respiratory infections. On the other hand, in dry, warm, equable climates acute respiratory diseases are less common so the patient living in these areas is less exposed to infection. There is nothing about any climate which will cure bronchiectasis but some people who cannot have surgery and who are economically able to make the change live longer and more comfortably in a climate such as that in the southwestern part of the United States.

The evaluation of results of treatment in this disease is in large part dependent upon the patient's opinion, so it is difficult or impossible to be strictly objective. We have arbitrarily placed each patient in one of seven categories. "No result" or "unchanged" is obvious. "Worse" indicates the patient to be in poor condition or having more symptoms than before therapy. Patients who died during or as a result of treatment are in this category although patients who died some months or years after treatment was begun are judged on their condition when last seen. Plus 5 is reserved for those patients who are completely cured, free from all symptoms and not handicapped or restricted in any activity. Plus 4 indicates patients free from demonstrable bronchiectasis.

but who may have minor symptoms not directly related to bronchiectasis or minor restriction of activity after treatment Plus 1, 2 and 3 indicate varying degrees of improvement from slight to moderately great, with or without any restriction of activity

One hundred ninety-four patients were treated and followed long enough to evaluate the results (Table 11) Length of follow-up ranged from one month to 12 years, 108 of them were followed in excess of 10 months, while only 40 were followed less than four months

The results of treatment in all patients is shown compared to the results in all surgically treated cases and in those with bilateral disease on whom a surgical procedure was carried out It is worthy of note that all cases classified plus 5 had surgery and in general the better results were produced in those patients undergoing operation

One surgical patient was not followed postoperatively, one has just been operated on and there is no opportunity yet to evaluate

TABLE 11
194 Cases Followed One Month to Twelve Years

Rate of Improvement	All Cases	Surgical Cases	Bilateral Surgical Cases
0	37	2	2
+1	39	1	1
+2	34	10	7
+3	36	21	8
+4	30	27	5
+5	11	11	1
Worse	7	3	1

TABLE 12
Results When Penicillin and Streptomycin Are Used

Rate of Improvement	All Cases	Surgical Cases	Nonsurgical Cases
0	6	2	4
+1	16	3	13
+2	15	9	6
+3	15	10	5
+4	17	16	1
+5	5	5	0
Worse	3	1	2

results Of the 3 classified as worse after operation, one described above developed advancing tuberculosis and eventually died about two years after lobectomy and one died suddenly on the second postoperative day and is the only operative mortality The other patient developed postlobectomy empyema, eventually required a thoracoplasty and finally when last heard from had had recurrence of cough and sputum In general, the surgical cases fall into the groups of better results while the nonoperated cases are evenly distributed through the less favorable classifications

Table 12 shows the results when penicillin was used Except for the fact that there were relatively few patients who had no improvement after using penicillin, no remarkable increase in the number of good results was apparent The addition of surgery to the treatment, however, causes a marked increase in the number of good results when compared to those treated with penicillin but without resection

The most difficult cases to treat are those who have severe bilateral disease It has already been indicated that in unilateral cases we favor surgery if at all possible When portions of both lungs are involved this becomes at times a matter for keen judgment Such patients are given full medical treatment and sinus surgery if indicated An effort is then made to evaluate a complete bronchogram, showing all lobes, and to judge as accurately as possible how much undiseased lung is present, whether the diseased lobes are being used at all for oxygen exchange and what percentage of the disease is in each lung We have found that if as much as 70 per cent of the bilateral disease is in one lung, removing that portion may permit sufficient improvement that resection of the remaining disease may be unnecessary Medical treatment, then, after the major portion of the infected focus is removed, may reduce cough or sputum to a tolerable minimum This is accomplished partially because of the improved general resistance and partially because the better lung is no longer bathed by purulent secretions spilled in from the other side

After such unilateral surgery on bilateral disease, the patient is followed carefully and six months to a year later roentgenograms and bronchograms are done to re-evaluate the problem Then, if symptoms warrant and sufficient vital capacity remains, an operation on the other side can be done In patients with bilaterally equal disease bilateral surgery is planned from the first but is still done in two stages, with six months to a year between and re-evaluation before the second operation In suitable cases both lower lobes, the right middle lobe and the lingula can be removed with enough vital capacity remaining in the upper lobes to permit practically normal life

It has been our experience that when one side of the chest is opened all the disease on that side must be eliminated. If even mildly bronchiectatic segments are allowed to remain they sooner or later become worse, no doubt in part at least due to the mechanical dilatation caused by overexpansion to fill the thoracic cavity. Then symptoms recur and secondary operations become necessary. The decision of how much lung to remove should be made prior to operation. The reason is amply illustrated by a case in which there was some discussion as to whether the lingula was diseased. At operation the surgeon could find no gross evidence of disease in this segment so only the obviously abnormal lower lobe was removed. A recurrence of symptoms prompted a review of the bronchogram which showed that the lingula was in fact dilated, and a secondary operation became necessary.

The postoperative course of patients having the first stage of bilateral operations is seldom as smooth as when all the disease can be eliminated at once. Collection of pleural fluid, difficulty in expanding the remaining lobe, excess bronchial secretions which are difficult to raise and may cause atelectasis are all frequently encountered and require diligence and speed to discover and treat promptly. A smooth and uncomplicated postoperative course is of more than minor importance because patients with complications, even though they eventually get well, frequently have thickened pleuras and reductions in pulmonary elasticity and



FIGURE 3



FIGURE 4

Fig 3 Bronchogram showing a bronchiectatic segment in each lobe later removed by multiple segmental resections—Fig 4 Bronchogram showing localized bronchiectasis in right lower lobe caused by aspiration of a head of timothy grass

chest wall or diaphragmatic movement which markedly reduce vital capacity and may be more of a handicap than would the sacrifice of a small segment of lung. For these reasons it is often wiser to perform total lobectomy rather than to attempt to save an undiseased segment. Segmental resections, good as they may be theoretically, are usually followed by more postoperative difficulties than are lobectomies. If the disease is widespread and bilateral, as much lung as possible must be conserved so that possible dangers of postoperative complications must be carefully weighed against the amount of lung to be sacrificed before making the important decision as to whether to do a segmental or total lobectomy. A man, aged 30, with multiple bronchiectatic segments in each lung illustrates perfectly the excellent result which may follow multiple segmental resections (Fig 3). On the other hand, one or two other patients have ended by losing an entire lung because of an attempt to save a segment not diseased at the time.

When pulmonary resection is being considered, the question frequently is asked as to whether if one lobe is removed the disease will develop in another lobe. This occurrence is distinctly uncommon unless there is an intervening acute episode of some type to act as a new etiologic factor. We have seen this occur in a patient who had not had a surgical procedure but who had severe disease in one lobe and mild disease in another as proved bronchographically. After two episodes of pneumonia the symptoms became worse and restudy with lipiodol showed the first lobe as before, the second severely involved and a third and previously normal lobe definitely bronchiectatic. In the several examples seen in which symptoms reappeared after surgery, a review of the bronchograms done preoperatively has always shown either disease previously present and not removed or an inadequate demonstration of the lobes not resected. It is for this reason that we now insist on thorough demonstration of all pulmonary segments preoperatively, at least on the side to be attacked.

Several special types of bronchiectasis deserve some mention. The inhalation of a foreign body is an occasional cause for bronchiectasis. Obtaining a history of such inhalation is often difficult for the memory of such an event may be clouded by many years of intervening symptoms. One patient in this series was discovered at operation to have a chicken bone lodged in the bronchus and only after this was revealed to him could he remember the event 17 years before when he choked. Foreign bodies may be completely nonopaque to the roentgenograms so the fact alone that nothing suggestive is visualized need not rule out this situation. One patient was found at surgery to have a head of timothy grass in a segmental bronchus in the right lower lobe. It had been inhaled

two years before and when postoperative pneumonia developed after appendectomy two weeks later, the persistent cough and sputum were assigned to that cause until a careful history suggested the possibility of the presence of a foreign body and lobectomy revealed the foreign material still *in situ* (Fig 4) That this may not be too uncommon is suggested by a recent report of 8 cases with this etiology⁴

Anything which obstructs, stenoses or interferes with bronchial drainage may instigate bronchiectasis. Congenital defects in bronchial distribution usually fall into this category and predispose to infection. Several such cases have been included in this series. Benign tumors such as bronchial adenomas have twice been a cause of dilated bronchi behind the obstructed area (Figs 5 and 6). A not uncommon cause for bronchiectasis limited to the middle lobe is stenosis caused by pressure on the bronchus from an enlarged lymph node. Although this may be an acute inflammatory node, even more common is a calcified tuberculous node which seems particularly prone to affect this bronchus. In eroding through the bronchial wall, it institutes the syndrome of middle lobe atelectasis and bronchiectasis (Figs 7 and 8).

Tuberculosis not infrequently involves the bronchial wall by direct extension. This may result in kinking or narrowing during the course of healing which, combined with fibrosis and contraction of the pulmonary parenchyma, also causes bronchial dilatation. When secondary infection is superimposed, it is difficult to distinguish this "tuberculous bronchiectasis" from the more common variety except that the former is more prone to occur in the upper lobes.



FIGURE 5

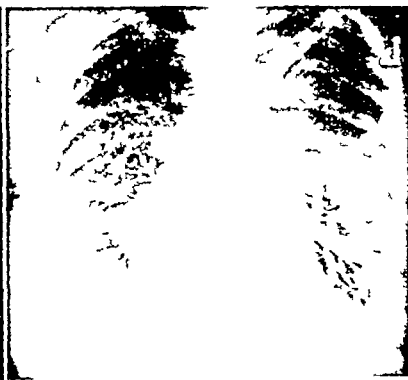


FIGURE 6

Fig 5 Roentgenogram showing small benign adenoma in left upper lobe with segmental area of atelectasis and bronchiectasis distal to it—Fig 6 Bronchogram demonstrating bronchiectasis in right lower lobe proved at lobectomy to be due to a bronchial adenoma

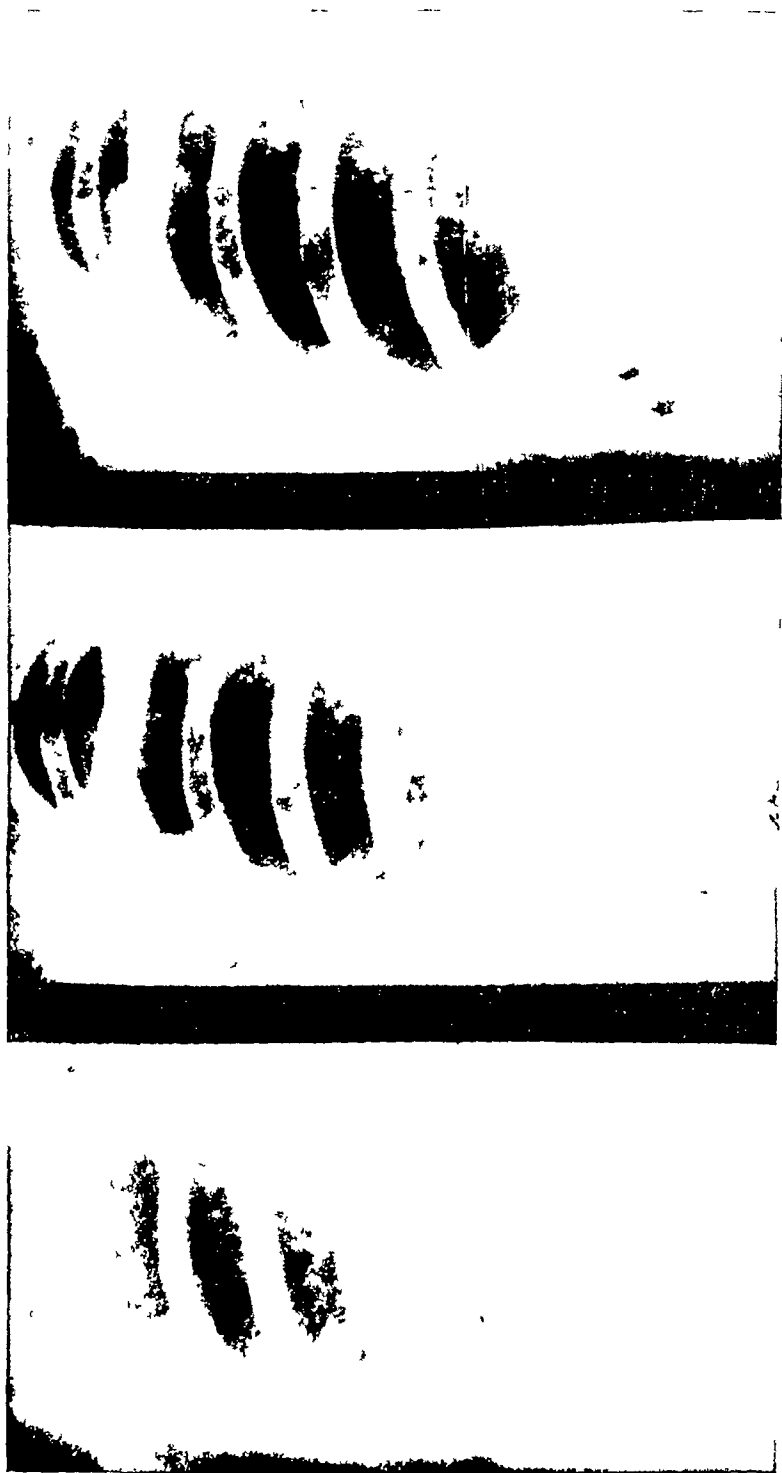


FIGURE 7 Calcified lymph node near right middle lobe bronchus in 1939 film (left) Area of pneumonitis and atelectasis beyond node in 1944 (middle) Broncholith has been coughed out leaving collapsed middle lobe in 1946 (right)

Much confusion still exists as to the relationship of congenital cystic disease to acquired cystic bronchiectasis. This is of little importance as the two are indistinguishable when fully developed. It is more important to realize that early in the disease before great thickening of the bronchial or cyst walls takes place the roentgenograms may show little or nothing abnormal. Only bronchography can confirm the diagnosis in these cases and again all lobes must be filled to avoid missing some of the disease (Fig 9).

Not all cases are accompanied by great amounts of sputum. Some are completely or almost completely "dry." In these cases the bronchi are dilated with relatively little thickening of their walls. Plain roentgenograms are often negative or inconclusive. Hemoptysis may be the only symptom calling attention to the condition. Sometimes only careful search with thorough bronchography will reveal the minimal dilatation in one small bronchial segment which is the source of bleeding.

Diseased segments of lobes are not too uncommon. Occasionally, scattered segments in several lobes are seen with the remainder of the bronchi being normal. One case, previously mentioned, had a diseased segment in every lobe. This problem was handled surgically in two stages by multiple segmental resections with excellent results.

The incidence and method of treatment of sinusitis have been



FIGURE 8

FIGURE 9

Fig 8 Atelectatic middle lobe containing saccular dilations of the bronchi not well shown in the reproduction—Fig 9 Right anterior oblique view to show particularly the bronchogram of left lung which contains cystic bronchiectasis in upper lobe including lingula and lower lobe. No evidence of disease in upper lobe was seen on plain roentgenogram.

noted Good results cannot be expected by treating the sinuses alone but neither will success follow the treatment of bronchiectasis, no matter how thorough, if the sinusitis is neglected If suppurative sinusitis is present it should be treated by whatever method is necessary, preferably before pulmonary resection is done Both the incidence of postoperative morbidity and recurring bronchial symptoms after eradication of the bronchiectasis will be reduced by this precaution

There is little correlation between the amount of sputum or severity of symptoms and the extent of disease as demonstrated roentgenographically Many patients with huge sacculations seem to have few symptoms and little toxicity On the other hand, an occasional patient has a great deal of diffuse bronchitis which causes much cough and sputum, yet bronchial dilatation is minimal These patients often respond well to medical treatment

The importance of vital capacity has been hinted Most patients with capacities below 1500 cc are poor risks for surgery However, if the diseased lobe is atelectatic it contributes little or not at all to respiratory function and its removal may cause little or no further reduction and the resulting freedom from cough and toxicity more than makes up the difference The removal of a non-atelectatic lung reduces the vital capacity by about one half Some remarkable improvements in vital capacity have taken place on treatment One woman with a vital capacity of only 800 cc was turned down for surgery Thorough treatment with penicillin and other medical methods has caused an increase in capacity to 1800 cc and the possibility of lobectomy on the worse side is now being considered Another patient had complete atelectasis of one lung with bronchostenosis and multiple bronchiectatic cavities Her disease was of lifelong duration and the vital capacity only 700 cc Medical treatment preoperatively brought it up to 1000 cc and after pneumonectomy it is now 1400 cc and she feels infinitely better In this case her vital capacity was doubled by removing one lung The answer to this seeming paradox probably is that the drowned lung preoperatively acted as a mechanical drag, preventing good expansion of the other lung, and the good lung was also constantly handicapped by being filled with pus from the infected side

Resected lungs or lobes almost invariably appear more diseased than would have been suspected by examining the patient, his roentgenograms or his bronchograms For this reason even minimal disease, if localized, is usually worthy of surgical removal These diseased areas are of relatively little use in oxygen exchange and constitute a constant hazard to future health Little stress has been placed on bronchiectasis as a focus of infection which

has a detrimental effect on other parts of the body. One of the patients in this series had a metastatic brain abscess from the diseased bronchi. Others have had arthritis apparently secondary to the disease, and several women with depressed ovarian function manifested by amenorrhea or infertility have responded after resection of the bronchiectatic lobe by resuming the menses or becoming pregnant. Frequent colds may be caused by bronchiectasis, whether owing to general reduction in immunity or localized lack of resistance in the respiratory tract.

In accord with good surgical principles, diseased areas must be totally removed if operated on at all, and surgery short of resection is always inadequate. Many years ago attempts were made to handle this problem by thoracoplasty, phrenic neurectomy or thoracotomy and freeing up the diseased lobe without resection. With few exceptions, these efforts were worse than useless and with the present state of development of thoracic surgery, are not to be condoned.

Throughout the entire period of this study evidence has accumulated that within the well recognized pattern of the disease numerous variations occur which make of each case a problem in itself. To achieve the best results in bronchiectasis it is necessary to realize that, aside from the patients who can be cured by radical resection of all the disease, improvement depends on a long term management of the many factors which contribute to each case. In this regard the intelligence, economic status and cooperation of the victim of the disease are as important as the doctor's interest, persistence, attention to detail and ingenuity.

SUMMARY AND CONCLUSIONS

Two hundred and seventy-seven cases of bronchiectasis observed by one individual have been reviewed. The chief complaint of half the patients was cough. Hemoptysis occurred at some time during the observation in over half the patients, and was the presenting symptoms of 33. Pneumonia had been present at some time in 159 cases. Plain roentgenograms were abnormal in 251 patients but in 20 were entirely normal.

A great variety of microorganisms occurred in the 93 sputa cultured, but either penicillin or streptomycin had a marked effect in altering the amount and characteristics of the sputum.

The methods of treatment have been discussed, with their indications and contraindications. Since surgical extirpation of the diseased area is the only method of cure this is advised unless contraindicated. The types of operations in the 78 patients handled by this means have been listed.

Medical measures of handling bronchiectasis have been described,

including a discussion of penicillin. The results have been classified in the 194 patients treated and followed from one month to 12 years. The most favorable outcome is obtained in those handled surgically, although some improvement occurred in most patients treated.

The method of handling bilateral cases surgically has been discussed in detail and these results compared to the general run of cases treated medically and surgically.

Unless it is possible to obtain a radical cure by surgery, bronchiectasis must be managed by a complete program carefully followed by the patient in full cooperation with an interested physician.

SUMARIO Y CONCLUSIONES

Se revisan 277 casos de bronquiectasis observados por una persona. El síntoma principal de la mitad de los enfermos fué la tos. La hemoptisis se observó alguna vez durante la observación en más de la mitad de los casos y fué la causa de ver al médico en 33 casos.

Se observó neumonía alguna vez en 159 casos.

Las radiografías simples fueron anormales en 251 enfermos, pero en 20 eran enteramente normales.

Una gran variedad de gérmenes en los esputos pudo observarse en los 93 esputos cultivados, pero ya sea la penicilina o la estreptomycin tuvieron gran influencia alterando la cantidad y características de ellos.

Se discuten los diversos tratamientos y sus indicaciones y contraindicaciones. Puesto que la extirpación quirúrgica es el único procedimiento curativo, se aconseja se adopte a menos que haya contraindicaciones. Los tipos de operaciones usados en 78 enfermos se indican.

Los procedimientos médicos empleados se describen incluyendo una discusión sobre la penicilina. Los resultados obtenidos en 194 enfermos tratados y vigilados durante un mes a doce meses se presentan clasificados. El resultado más favorable es el obtenido por los procedimientos quirúrgicos si bien todos los tratados mejoraron en general.

El procedimiento para tratar los casos bilaterales es motivo de comentario en detalle y sus resultados son comparados con la evolución general de los tratados quirúrgicamente y por procedimientos médicos.

A menos que sea posible obtener una curación radical por la cirugía, la bronquiectasis debe considerarse en su terapéutica bajo un programa completo que debe ser seguido completamente por el enfermo cooperando con el médico interesado.

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A Method for Topical Anesthesia by Nebulization of Local Anesthetics[†]

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The number of procedures involving the direct examination of, and the introduction of instruments and materials into, the tubular structures of the respiratory tract is increasing. This increase in endoscopic procedures has been attended by greater efforts to overcome the natural defenses of the entrance to the respiratory passages. The defenses are ¹

- 1) The swallowing reflex, originating chiefly in the posterior pharynx, dorsum of the tongue, and pyriform sinuses

- 2) The gag reflex, originating chiefly in the anterior faucial pillars, soft palate, uvula, epiglottis, and posterior pharynx

- 3) The cough reflex, originating chiefly in the larynx, trachea, and carina

- 4) The anatomic position and structure of the larynx, at right angles with the oral cavity, below the epiglottis, and with the strongly contractile glottis at its entrance

- 5) The patient's general apprehension concerning instrumentation of the respiratory passages

The most commonly practiced method of reducing the patient's apprehension is by preliminary sedation and a brief explanation of the necessity for relaxation and cooperation. The reflex defenses are usually attacked by administering a surface anesthetic. The anatomic peculiarities of the larynx constitute a major difficulty in introducing anesthetic solutions as well as instruments and other materials.

The conventional technique of obtaining surface anesthesia consists of "boldly squirting 2 or 3 cubic centimeters from a syringe (or atomizer) through the mouth on to the posterior pharyngeal wall, after which the anesthetist side-steps smartly out of the line of the patient's mouth and relies on the violent gagging and coughing to spread the liquid throughout the pharynx and larynx."² It is usually necessary, in addition, to swab the

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anterior pillars and pyriform sinuses with cotton pledgets soaked in the anesthetic solution, and finally to inject more of the solution into the larynx through a curved tracheal cannula under laryngoscopy. The anesthesia which results is often inadequate for bronchoscopy, necessitating the application of additional solution directly onto the carina through the bronchoscope.

The disadvantages of this technique are apparent. It requires an excessive quantity of the drug, several specialized instruments, and a technically skilled operator. It is distasteful to the patient and time-consuming to the physician. Consequently there has been a concerted attempt to develop a technique which secures adequate and widespread anesthesia without these disadvantages.

Perhaps the most precise modification of the conventional method is that described for laryngoscopy by Jackson,³ who atomizes the pharynx and right faucial pillar for one or two seconds with 10 per cent cocaine. He then introduces three or four drops of the solution into the larynx under mirror visualization, and after 3 minutes repeats this amount. Jackson states that it is essential that every drop from the syringe be seen to enter the larynx in order to obtain adequate anesthesia from such a small amount of solution. For bronchoscopy, he mentions the additional application of a small quantity of 4 per cent cocaine through the bronchoscope. While the amount of solution employed in his procedure is small, all the other disadvantages are still present. The accurate placement of each drop of solution depends on a dexterity that few operators possess.

Another modification using small dosage has been described recently by Carabelli⁴ who employs 0.25 per cent pontocaine. He uses a total of 8 cc of solution, first spraying into the pharynx through a micro-atomizer, then instilling the balance into the trachea through an endotracheal catheter. Its chief advantage is that it is one of the few techniques in the literature that does not exceed the recommended dose of the drug. Its main disadvantage is that it involves introducing an endotracheal catheter. Furthermore, our work with fine particle atomizers disclosed that the disadvantages inherent in the use of ordinary atomizers were not completely overcome.

The disadvantages encountered in spraying via the mouth led to an investigation of the nasal route. Adams,⁵ Slater,⁶ and Carr and his associates,⁷ have described techniques of instilling the anesthetic solution through a nostril while the tongue is held to prevent swallowing. When the solution reaches the glottis, coughing occurs, continued administration followed by further coughing finally results in anesthesia which is adequate for injecting iodized oil through the same nostril for passive bronchography. The use

of this technique reduces but does not eliminate the patient's discomfort, it may be used for bronchography, but is not applicable to endoscopic procedures

A technique described by MacIntosh² utilizes a rubber nasal catheter with an atomizer tip. The catheter is used to direct the atomized cocaine into the nasal and pharyngeal passages, being gradually advanced through the nasopharynx as anesthesia is obtained, and finally passed into the larynx for endotracheal anesthetization. He states that a cough is a sure sign that the spray has found its target. Thus the technique involves discomfort to the patient, and requires skillful manipulation to pass the catheter into the larynx. Rowbotham,⁸ Kenton,⁹ and Harang¹⁰ have each designed different instruments or procedures which are subject to the same disadvantages as those described.

Still another route of administration has been employed by Armand-Delille,¹¹ Guy and Elder,¹² and Grady.¹³ They insert a cannula through the skin of the neck and the cricothyroid membrane directly into the larynx after local infiltration of these tissues with 0.5 per cent procaine. A topical anesthetic is then injected through the cannula, producing a paroxysm of coughing which serves to spread the agent throughout the area to be anesthetized. Iodized oil may then be injected through the same cannula to obtain bronchograms. This has been described as an excellent technique for bronchography in small children, but seems somewhat radical in approach with potentially grave complications.

The technique designed and originally described by us¹⁴ is based on nebulization of the surface anesthetic solution. By having the patient inhale the mist under certain conditions, a profound surface anesthesia is obtained which extends from the external nares and mouth to the finest bronchioles. Other authors^{2, 15, 16} have noted the logic of the use of nebulizers in obtaining surface anesthesia, but have not described a detailed technique or a tabulation of results.

It is important to distinguish nebulization from atomization. Ordinary atomization is the production of a spray of relatively large droplets travelling at high speed. When this spray strikes the sensitive areas of the pharynx which must be reached to obtain adequate anesthesia, it usually results in gagging, retching, and coughing, as previously pointed out. In nebulization the largest droplets are baffled out within the nebulizer, resulting in a fine mist of particles that may be inhaled comfortably and carried by convection into the deeper bronchial passages.¹⁷ This method overcomes all the defenses of the respiratory system, without the disadvantages of the conventional method of anesthesia or its modifications.

Materials

The essential instrument is an adequate nebulizer. We have found some nebulizers to be inadequate. The following properties of the nebulizer are desirable.

1) Efficiency of nebulization. The delivery of aerosol by the nebulizer must be sufficiently rapid. Many nebulizers are inefficient, i.e., the amount of liquid delivered per unit volume of gas passing through the nebulizer is low, and adequate anesthesia is difficult to establish.

2) Construction of the nebulizer. The well of the nebulizer must be capacious enough to accommodate 8 cubic centimeters of solution. It must also be so constructed that tilting the nebulizer *does not easily spill the solution out of the neck of the nebulizer into the patient's mouth*, since rapid absorption of surface anesthetics may result in toxic reactions.

3) Particle size distribution. The aerosol produced by the nebulizer must consist of particles which are below the size range that produces reflex gagging, and yet not so small that they remain suspended and are exhaled (approximately 0.5 micron and smaller). The ideal particle size range for surface anesthesia is 0.5 to possibly 5 micron in radius. Within this range, the majority of particles should be small enough (0.5 to 2 micron) to be carried by convection and deposited in the bronchial tree. A substantial amount of the aerosol, however, should consist of intermediate sized particles (2 to 5 micron) that will be deposited by centrifugal force in the pharynx and larynx.

Some nebulizers produce too high a percentage of larger droplets that are unable to traverse the pharyngo-laryngeal angle without deposition on the posterior pharynx, and hence fail adequately to anesthetize the bronchial tree. These nebulizers are little better than atomizers in their final results. Other nebulizers produce an aerosol consisting almost entirely of particles so small that they uniformly reach the bronchial tree, but fail to anesthetize the pharynx and larynx adequately through lack of sufficient particles of intermediate size.

This phenomenon has been studied exhaustively by nebulizing known quantities of PSP from various nebulizers, to the delivery ends of which are attached right-angle L tubes. The amount of PSP remaining in the nebulizer and the amount deposited in the L tube after nebulizing under uniform conditions can be determined colorimetrically. From these figures can be calculated the per cent delivery of the nebulizer and the per cent deposition of intermediate sized particles in the L tube.^{18, 19}

A nebulizer that fulfills the requirements for use in surface

anesthesia, both clinically and in laboratory studies of particle size distribution is the De Vilbiss No 40 Intermediate sized particles comprise 15 to 20 per cent of the total delivery This model was used for all cases herein reported

Oxygen or air may be used to nebulize the solution An oxygen tank with attached flow meter, or an air compressor will suffice Oxygen was used routinely for these cases because of its availability and convenience The pressure was transmitted to the nebulizer through ordinary gum rubber tubing

A simple mouthpiece for the nebulizer consists of a segment of rubber tubing three inches long and one-half inch in diameter (Fig 1) It is pushed about one inch onto the oral end of the nebulizer so that the point of delivery of the aerosol is extended about two inches into the mouth This is an important step in procedure as it prevents the patient from unwittingly baffling out much of the aerosol by partially occluding the mouth of the nebulizer with the teeth or tip of the tongue

In performance of bronchography, lipiodol is often instilled through the nose and allowed to flow passively into the bronchial tree In such cases, nasal tips* may be attached to the

*The nasal tips and the nebulizer are included in the De Vilbiss No 640 combination

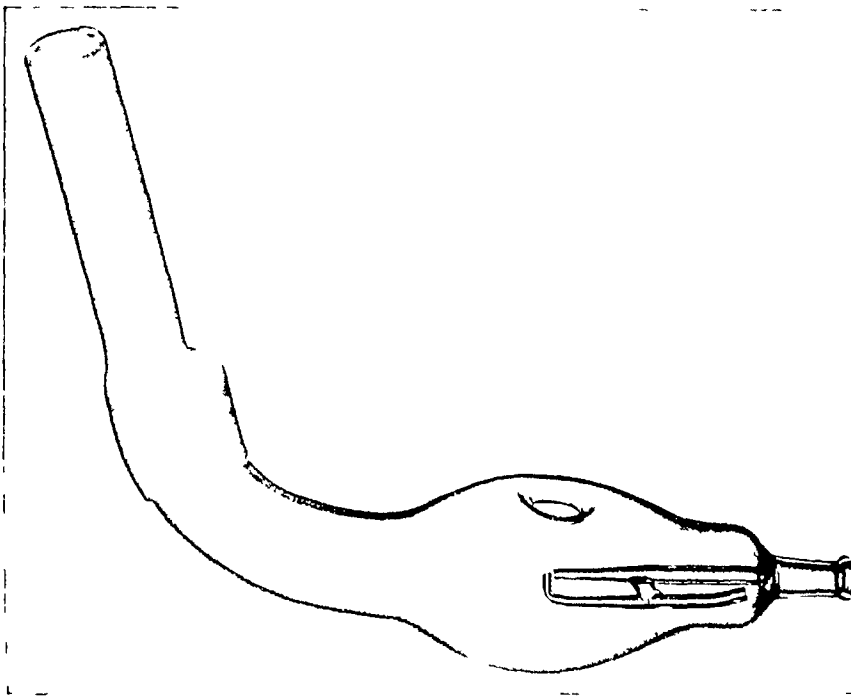


FIGURE 1 DeVilbiss No 40 nebulizer with rubber mouthpiece

nebulizer and the first half of the anesthetic solution inhaled through the nose to insure anesthesia of the nasal and nasopharyngeal mucosa

The anesthetic solutions preferred are 0.5 per cent pontocaine and 4 per cent cocaine. After extensive experimentation it was found that stronger solutions were unnecessary, and weaker ones inadequate. One minim of epinephrine 1:1000 is added for each cubic centimeter of solution to delay absorption. When cyclopropane anesthesia is to follow, the epinephrine is omitted to prevent a possible cumulative irritation of the cardiac musculature.

The only other materials employed are those necessary for maintaining proper precautions whenever surface anesthetics are used, viz. sodium pentothal, epinephrine, a suction machine, and apparatus for administering oxygen and artificial respiration.

Premedication

Our patients are usually premedicated with nembutal two hours before, and morphine and atropine one hour before anesthetization. The dosage may be varied to suit the individual patient or the preference of the physician, and substitutions such as demerol, codeine, scopolamine, etc., are perfectly compatible with good results. However, either atropine or scopolamine should always be employed, as copious secretions tend to dilute the anesthetic agent, and the concentration of these agents is already minimal. The premedication serves the purpose of sedating the patient, minimizing apprehension, inhibiting secretions, and combating the side reactions of the anesthetic agent.

Method

The patient is seated, his nose is occluded by adhesive tape, and he is instructed to relax and simply breathe through his mouth. Eight cubic centimeters of anesthetic solution are introduced into the nebulizer and the oxygen flowmeter adjusted to approximately 6 to 8 liters per minute for continuous nebulization. Generation of aerosol continuously is more wasteful than generation only during inspiration, but it allows the use of a single technique on patients of all ages and degrees of ability manually to operate a Y tube.

The production of aerosol is demonstrated to the patient, and it is explained that he is to inhale the mist. The nebulizer is inserted into the patient's mouth in such a way that the delivery end of the rubber mouthpiece is well into the back of the mouth. As the patient is inhaling the aerosol, he is prepared for the sensations of surface anesthesia by explaining that soon his tongue will become numb, he will feel a "lump" in his throat, and he

will finally be unable to swallow. He is then instructed in the proper method of holding the nebulizer and he continues to do so for 30 minutes.

During the first five minutes the tip is allowed to point straight back toward the uvula. Then the anterior faucial pillars are anesthetized by turning the nebulizer 30 degrees for five minutes to each side in turn. For the second 15 minute period, the patient holds his own tongue forward with a gauze sponge, introduces the nebulizer tip as far back as possible, and aims toward the larynx and the pyriform sinuses for five minutes each. The entire procedure requires 30 minutes. In this way, the aerosol reaches not only the deeper bronchial structures by convection, but also the sensitive areas of the pharynx and larynx by direct impact. After the preliminary instruction, the patient continues his own anesthetization without fear or apprehension, and immediately at the end of nebulization is ready for the endotracheal or endobronchial procedure. The entire technique requires about five minutes of the anesthetist's time. The anesthetist therefore, is free to do other work in the 25 minutes remaining while the patient administers his own anesthetic under supervision.

Modifications of Technique

1) For recumbent patients. Our experience with surgical patients has been predominantly with cases requiring endotracheal intubation for the administration of general anesthetics. It is generally agreed² that topical anesthesia is preferable or is a



FIGURE 2A

FIGURE 2B

Fig 2A Bronchogram of a 5 year old child with bronchiectasis of the right upper lobe—*Fig 2B* Bronchogram of a 10 year old child with bronchiectasis of the right middle lobe

desirable supplement to general anesthesia for the introduction of the endotracheal tube. Since the patients are routinely wheeled into the hall or foyer of the operating room on stretchers to await their turn on the operating table, a convenient place and time for administration are available. The nose is taped off and the patient's head rotated to one side and the mouthpiece introduced by an assistant as described above. Because of the sedation and reclining posture, the patients often doze throughout the procedure.

2) For small children. Children above the age of four or five years use the same techniques as described for adults. For younger children, the entire procedure is carried out with the child sitting on the lap of a nurse, who cuddles the child in one arm and places the straight rubber tip of the nebulizer in the child's mouth as though administering a bottle feeding. The younger child has a feeling of security when handled in this way, and the elements of fear and apprehension are almost completely absent. The use of nebulization anesthesia was originally conceived for the purpose of obtaining bronchograms in children with chronic pulmonary diseases and our experiences with this method have been gratifying (Fig. 2).

Results

The procedures performed with this technique include bronchography, bronchoscopy, bronchosprometry and endotracheal intubation. In order to have all participating physicians evaluate cases uniformly, four degrees of response were formulated. An excellent

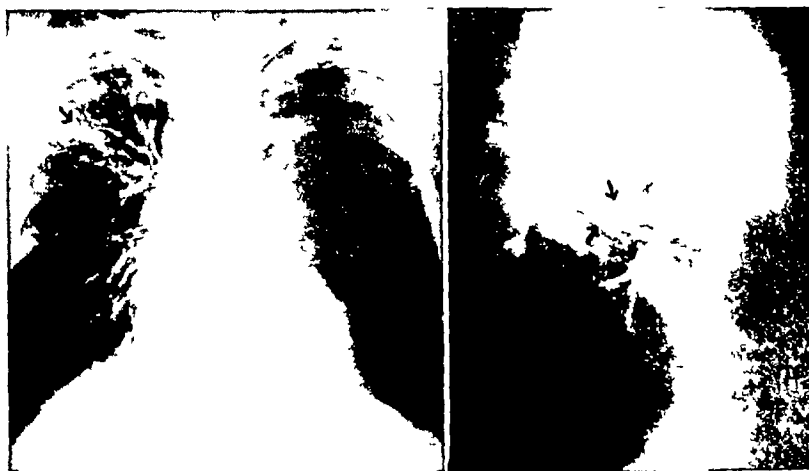


FIGURE 2C

FIGURE 2D

Bronchograms of an adult demonstrating the entire bronchial tree with filling of what is probably an epithelialized tuberculous cavity.

result was considered one in which there was absolutely no gag or cough during the entire endotracheal or endobronchial procedure, a condition that is infrequently obtained by conventional methods. For bronchoscopy this classification had to be slightly modified as it was observed that an occasional patient emitted a single mild coughing effort when the bronchoscope reached the carina. A good result was one in which there was slight gagging or coughing which immediately subsided and did not interfere with the endoscopic procedure. A fair result was defined as one in which there was occasional repeated gagging or coughing. A poor result was one in which marked gagging and coughing occurred throughout the procedure. The vast majority of results fell into the classification of excellent, and the balance were good. There were no fair or poor results recorded by any of the operators, when using the technique exactly as described.

This is apparently the simplest technique devised for obtaining surface anesthesia of the entire respiratory passage. It requires no operative skill or manipulative ability, and no expensive or specialized instruments. All the materials are standard hospital equipment except the nebulizer, which is available at almost any pharmacy. A profound and evenly distributed anesthesia is obtained throughout the lower as well as the upper respiratory tract with no discomfort to the patient. The anesthesia is always as good as that obtained by conventional methods and in most cases better.

The time required of the anesthetist is less than in other methods, as the patient administers the greater part of the anesthetic to himself. Even when the patient is necessarily recumbent, the modified technique allows the anesthetist to circulate in the close vicinity of the patient while an assistant trained in the signs of toxicity holds the nebulizer and stands watch by the stretcher.

Aside from the medical and technical aspects, one of the greatest advantages is the absence of discomfort to the patient. There is no gagging, coughing, or spitting associated with its use. Finally the likelihood of toxic reactions is greatly diminished. The retention of various aerosols administered in the manner described has been reported by several authors to be of the order of 6 per cent,²⁰ 15 per cent²¹⁻²² and 25 per cent²³. In attempting to evaluate per cent retention of aerosols when administered as described, one of us (J B M) inhaled a solution of phenolsulphonthalein, using the method of Abramson, and found that the total urinary excretion was 14.57 per cent after 16 hours. Even assuming that the retention is as much as 25 per cent of the 8 cubic centimeters, the actual amount absorbed is only 2 cubic centimeters. This is the equivalent of 0.5 cubic centimeters of 2 per cent pontocaine,

or 0.8 cubic centimeters of 10 per cent cocaine, well below the toxic dosages of these drugs. Furthermore, the absence of large drops and pools of solution in the pharynx and mouth, plus the drugs and anesthetics administered to prevent the accumulation of saliva and to abolish the swallowing reflex, completely eliminates swallowing the toxic solutions.

The chief criticism of the procedure is that it is time consuming. It is true that a cooperative patient can be anesthetized more rapidly by some of the other methods. However, perusal of medical writings reveals the fact that many authors recommend a period of 20 to 30 minutes to obtain satisfactory anesthesia, and that one of the most frequent causes of poor anesthesia is failure to take sufficient time to apply the solution and await its maximal action.² In attempting to hasten the procedure, we have used stronger anesthetic solutions for shorter periods of time, and found that the anesthesia produced was not as widespread as that produced by using the recommended strengths for the full 30 minutes. This phenomenon is probably due to the small size of the particles produced by nebulizers, and the consequent slow surface coverage of the areas involved. This can be illustrated by aiming an atomizer spray and an aerosol of PSP toward filter papers that have been soaked in 10 per cent sodium hydroxide. Instead of reddening immediately as does the atomized paper, the nebulized paper gradually turns faintly pink and over a surprisingly long period of time finally becomes red.

There are apparently no dangers inherent in this method. The use of surface anesthetics always carries an element of risk^{24, 26} and reactions may occur in children and hypersensitive patients even with the use of minute amounts of drugs. Only one such reaction has occurred in our series. Early in the study, while using 2 per cent pontocaine, a 1½ year old colored girl began convulsing while being anesthetized for bronchography. Fortunately, she responded to the administration of intravenous barbiturates and oxygen inhalation, and suffered no ill effects.

The limitations of this method for topical anesthesia by nebulization of local anesthetics are as yet indefinable. Its use has met with success in many procedures requiring surface anesthesia of a widespread distribution by gentle application. In addition to the endoscopic aspects of surface anesthesia, it has been used for temporary relief of sneezing, the pain of severe pharyngitis and laryngitis, and for intractable coughing in tracheitis, bronchitis, and pertussis.

We are indebted to H. Bertel, M.D., attending anesthetist, for invaluable assistance and advice. For contributing cases and aiding in the

Diagnostic Bronchial Lavage in Tuberculosis*

MARCIO MULLER BUENO, M D , F C C P **

Fall River, Massachusetts

Diagnostic bronchial lavage in tuberculosis consists of washing of the tracheo-bronchial passages in order to search for tubercle bacilli. In patients who do not raise or who have negative sputa, gastric washings are often used. However, the gastric lavage does not satisfy completely and other tests have been tried: laryngeal swabs, search of bacilli in secretions collected through bronchoscope or through nasal tubes. de Abreu^{1 12} in 1944, first tried diagnostic bronchial lavage in tuberculosis. He used injections of saline through the crico-thyroid membrane about 40 times with one fatal accident due to anesthesia. Fernandes^{27 28} was the first to use the supraglottic method.

Technique

Bronchial lavage is easily performed, it is simpler than gastric lavage. Furthermore, it is tolerated better by the patient. The supraglottic region is anaesthetized by spraying it with a solution of 2 per cent pontocaine or 4 per cent cocaine. The spraying is done twice, with an intervening interval of 2 or 3 minutes, each application consists of eight to 10 ejections from an ordinary atomizer. The patient, while seated, should hold his tongue and breathe deeply. When he perceives a numbness on swallowing, the saline solution or sterile water is introduced. The patient's tongue is held with a piece of gauze between the thumb and index finger and the chin between the index and third finger of the physician (Fig 1). With the tongue out and fixed, the patient cannot swallow and the fluid enters the trachea and bronchi. The patient breathes rapidly (panting) while 20 cubic centimeters of fluid is introduced in two periods. Immediately the patient expels some of the fluid and later on, bending forward, coughs and expectorates the rest.

Bacilli are sought in the collected fluid by direct smears, cultures and animal inoculation.

The impression that bronchial lavage gives positive results only when the lesions are in the lower parts of the lungs is erroneous.

*From the Fall River Tuberculosis Hospital, Fall River, Massachusetts. Presented at the 14th Annual Meeting, American College of Chest Physicians, Chicago, Illinois, June 17-20, 1948.

**Medical Director, Fall River Tuberculosis Hospital, Fall River, Mass.

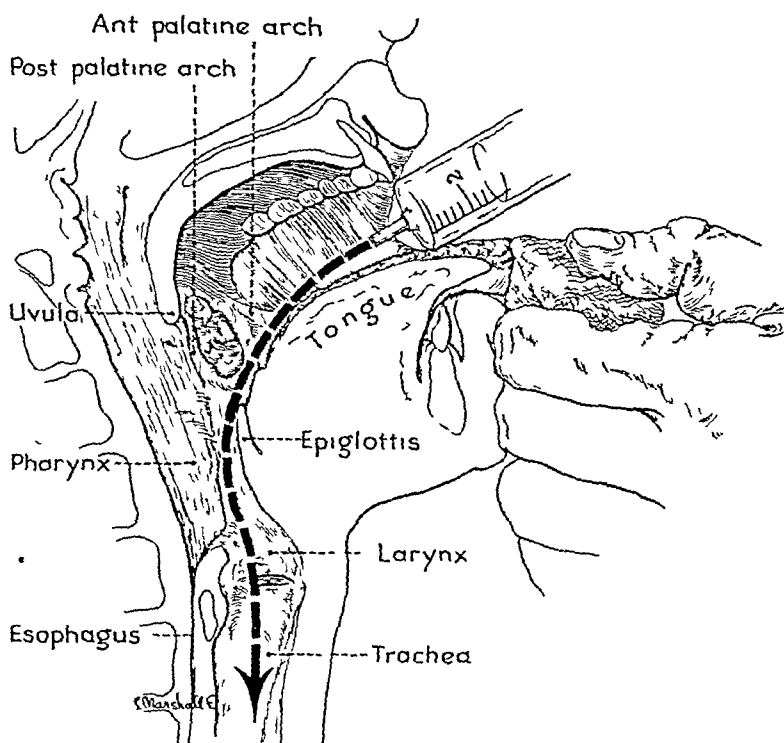


FIGURE 1

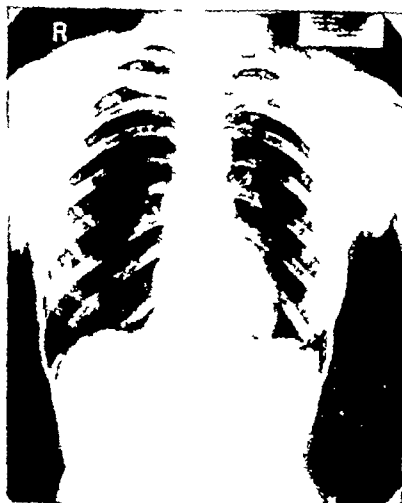


FIGURE 2



FIGURE 3

Fig 2, M.J. Infiltration left apex. Positive bronchial lavage. Negative gastric. No symptoms.—Fig 3 L.R. Left thoracoplasty April 1947. In 1948 two negative gastric lavages. Positive bronchial.

In 39 cases at Sassaquin Sanatorium, 15 positive results were obtained and in 12 the lesions were located only in one or both upper lobes

Innocuousness

Bronchial lavage is harmless About 200 have been performed in the United States and no accident has been reported Over 3,000 lavages have been performed abroad In Brazil, where the test first was tried, 2,000 have been done Correa,²⁵ in Brazil, reported no serious accident, but 31 per cent of his patients presented allergic symptoms following the lavage Usually the symptoms were mild and headaches prevailed Fernandes^{27 28} reported pain in the chest which lasted a few days following the lavage in 8 per cent of his patients He thought the pain was caused by small foci of alveolitis I have never observed such symptoms and neither has de Abreu¹⁻¹² in his 1,741 lavages The fear of the disease spreading, as it may following hemoptysis, is baseless Only cases of apparently inactive or of low grade activity receive bronchial lavage

Contra-Indications

Because this procedure needs the close cooperation of the patients, it is withheld from children under 12 years of age In patients with severe impairments of pulmonary functions, hemop-

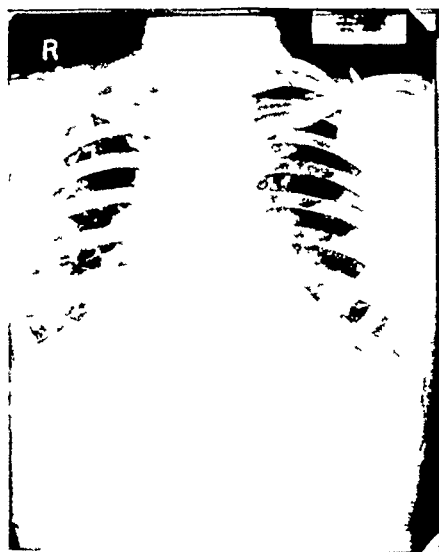


FIGURE 4



FIGURE 5

Fig 4, C R Fibrosis right apex Last positive sputum September 1946, concentration Since then, negative gastric, positive bronchial, January 1948—Fig 5, J H Four years of left pneumothorax Positive gastric in January 1948 Negative bronchial Failure of bronchial lavage

tysis (Castillo²¹⁻²³), cardiac decompensation and bronchial asthma this procedure is contra indicated

Must we try bronchial lavage if we already have a gastric lavage? The advantages of bronchial over gastric lavage are (1) Technique easier for the physician, (2) Better tolerated by the patient, (3) Can be done at any time Gastric should be done before breakfast and it must be performed as soon as he awakes, (4) The patient cannot deceive the physician as he can with a gastric lavage, (5) The acid-fast bacilli are not destroyed as they are by the gastric juice when stomach washings are not properly treated

Comparison Between Bronchial and Gastric Lavage Showing Number of Negative and Positive Findings and Per cent of Positives

		Gastric	Bronchial
1	1944—Rio de Janeiro, Brazil R. Fernandes and W. Hirsch ²⁹ Hospital Miguel Pereira 18 cases	Negative 17 Positive 1 5.55%	10 8 44.44%
2	1945—Buenos Aires, Argentina A. P. Heudtlass, J. A. Marti, A. Adamo ³⁴ 70 cases	Negative 70 Positive 0 0.00%	66 4 5.75%
3	1946—Verona, New Jersey Marcio M. Bueno Essex County Sanatorium 10 cases	Negative 9 Positive 1 43.7%	4 6 60%
4	1947—Rio de Janeiro, Brazil M. Fontes Magarao and H. Linhares ⁴⁰ Tuberculosis Lab, Rio de Janeiro 1,400 cases (2 groups)	Negative 590 Positive 110 16%	570 130 19%
5	1948—New Bedford, Massachusetts Marcio M. Bueno Sassaquin Sanatorium 39 cases	Negative 34 Positive 5 12.08%	24 15 38.48%
6	1948—Chicago, Illinois J. S. Bornstein ¹⁷ Winfield Hospital 26 cases	Negative 22 Positive 4 15.3%	22 4 15.3%
7	1947—Utrecht, Holland K. Magnus and Van der Holden ⁴¹ Dennenoord and Amerongen Sanatoria 73 patients—266 cultures (gas and br)	Negative 75 Positive 58 43.6%	35 98 73.3%

In the 11 studies shown in the table, only two revealed a larger number of positive results in gastric than bronchial lavage. Number 10 is not a good example since only direct smears were made without cultures or inoculations. In number eight on inoculation, the gastric was more sensitive than the bronchial lavage. In number six Bornstein states, "Bronchial lavage is as sensitive as gastric lavage when the latter is done under optimal conditions. Bronchial lavage is another weapon to be used in detecting

Comparison Between Gastric and Bronchial Lavage			
Cases			
8	1946 J C Rey and Abel Cetrangolo ⁴³ Buenos Aires, Argentina	99	Direct smears and cultures— same proportion of positive results Inoculation in guinea pig gastric—47% positive bronchial—34% positive
9	1945 A Chapchap and O V Cordeiro ²⁴ Sao Paulo, Brazil	39	Direct smears only—29 negative with both procedures 10—23% positive bronchial 15 3% positive gastric
10	1945 R Brandi and J A B da Fonseca ¹⁹ Sao Paulo, Brazil	100	Direct smears only 76 98% positive gastric 63 36% positive bronchial 82 30% positive both procedures
11	1945 S A Sarmiento ⁴⁵ Buenos Aires, Argentina (intralaryngeal injection)	19	Direct smears Bronchial—3 positive Gastric—0 positive Cultures—(11 cases) Bronchial—4 positive Gastric—3 positive Inoculation— Bronchial—11 positive Gastric—8 positive

Bronchial Lavage
Percentage of Positive Results

	Number of lavages	Positive	Per cent
Manuel de Abreu ¹⁻¹² (from August 1, 1944 to December 31, 1947)	1,741	293	16.8
Juan Castillo ²¹⁻²³	500		90
J S Bornstein ¹⁷	75	12	16
M M Bueno	65	17	26.15
Magnus and Van der Holden ¹⁴	133	98	73.3
D'ovidio and Bellingeri ²⁶	366	78	20.86

tubercle bacilli in pulmonary diagnostic cases and in following quiescent or presumably arrested tuberculous cases in the office, clinic or out-patient" In numbers one, three and five, gastric lavages were done under "optimal conditions" In my cases only guinea pig inoculations were used Fernandes^{27 28} employed direct smears, cultures and inoculations Magarao and Linhares⁴⁰ used direct smears and cultures (Loewenstein's medium) Bornstein¹⁷ employed direct smears and cultures (Petragnani's medium)

Results at Sassaquin Sanatorium, New Bedford, Massachusetts

	Number of cases	Positive Bronchial	Positive Gastric
Suspected tuberculosis (on admission) *	17	5	2
Apparently arrested (on discharge)	18	8	1

*Suspected tuberculosis—cases of non-apparent, asymptomatic, pulmonary tuberculosis found either by mass x-ray survey done at the city clinic or by induction in the service

CONCLUSION

Bronchial lavage has a definite place among the tests to detect tubercle bacilli In patients suspected of pulmonary tuberculosis by x-ray, diagnostic bronchial lavage should be routine Even if the gastric lavage were as sensitive as bronchial, the "optimal conditions" would make the former impractical In mass x-ray surveys when minimal lesions are found bronchial lavage is the test of choice Among cases for discharge from hospitals, a definite policy should be adopted in regard to tests Almost every hospital differs The most important is the interpretation of the clinical and radiological findings

The danger of infection from gastric lavage-positive people is practically nil This subject deserves further investigation

CONCLUSION

El lavado bronquial tiene un lugar definido entre los procedimientos de investigación del bacilo de la tuberculosis En los enfermos sospechosos de tuberculosis el lavado bronquial con fin diagnóstico debe hacerse de manera rutinaria Aun en el caso de que el lavado gastrico fuese tan sensitivo como el bronquial, las "condiciones óptimas" harían el primero no práctico En los catástrofes roentgenologicas, cuando se encuentran lesiones mínimas, el lavado bronquial es el procedimiento de elección Entre los casos de alta de los hospitales, el lavado bronquial debe ser de rutina

El peligro de infección por las personas que tienen lavado gastrico positivo, es practicamente nulo Este asunto merece investigación ulterior

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D I S C U S S I O N

HAROLD GUYON TRIMBLE, MD, F C C P

Oakland, California

We became interested in this procedure some two years ago but did little about it until a few months ago I can subscribe to what Dr Bueno has told you, definitely The problem from our standpoint is that we make every attempt to obtain tubercle bacilli, to be sure the disease in question is really tuberculosis, as well as to guide the course and duration of collapse therapy In follow-up it is necessary to know the status of the patient's output of tubercle bacilli as well as surveying serial x-ray films Life is getting complicated, formerly we said "this is our opinion," but now we endeavor to get the organisms

The difficulty with gastric lavage is as stated The technic must be meticulous and even in hospitals we have great difficulty in getting an intern to the patient before he is awake, before he smells food, before there is activity in the ward (because some wards start out pretty early) All these things stimulate gastric peristalsis and interfere with obtaining a positive gastric specimen

A simple office procedure such as tracheal lavage is helpful

because it is difficult to get a dependable gastric lavage. If proper material is not obtained one cannot depend on negative results.

One other thing that has been of value. We can get positive cultures in as short a time as five days with some of the new technics, and many times within a week. We call our procedure not bronchial but tracheal lavage, because our procedure is more nearly that. However, as Dr. Bueno brought out that is probably a matter of the depth of the local anesthesia. Under deep anesthesia the patient should be bent over rather quickly to get the salt solution back. Otherwise within a little while it mostly disappears.

The details as Dr. Bueno has described them to you are important. They are simple. The doctor can do tracheal lavage in his office, in the hospital or sanatorium. It can be done at any time of the day. We have had no untoward results.

This procedure can be recommended because it is simpler than gastric lavage, equally effective and can be done more readily and at almost any time of day. The more we will use tracheal lavage the more we will know about our patients, with correspondingly better longtime results.

J. S. BORNSTEIN, M.D.
Chicago, Illinois

We have used this procedure in the office, the out-patient department, the clinic and the hospital. In my opinion there is a tendency to be somewhat over-enthusiastic about it. We had no untoward reactions in about 100 cases, but the method is just an adjunct to all other diagnostic procedures. I think it is more complicated than gastric lavage because one has to use topical anesthesia and that requires about 15 minutes in some patients, depending on personality. In some instances if one uses 2 per cent solution of cocaine or any of the other local anesthetics one can get material for culture from just using 1 or 2 cc of cocaine dropped into the trachea. Cuthbert, an English phthisiologist, has shown that if one merely swabs the vocal cords, one can get a positive culture, and probably some of these positives come from tubercle bacilli on the vocal cords. It is important to determine when to terminate treatment, because I am sure that following thoracoplasty one can get positive bronchial lavages in almost any case. Termination of treatment is a matter of clinical judgment, and the fact that two or three tubercle bacilli can be recovered by bronchial lavage is not always important. In these days when calcification and pulmonary infiltration of unknown etiology are recognized, bronchial lavage is of value in detecting

tubercle bacilli, it is also a method of detecting various fungi. As a further aid, it may be of possible value in the detection of early bronchogenic carcinoma where the malignant growth is in one of the terminal segments. That remains to be proved. This suggestion may be of some interest in future investigations.

GEORGE W. HOLMES, M.D., F.C.C.P.
Chicago, Illinois

Our work on bronchial lavage at the Municipal Tuberculosis Sanitarium in Chicago has been rather limited, principally because it requires as much anesthesia to do an efficient bronchial lavage as to do a bronchoscopy. Therefore we have felt that by doing bronchoscopy and making a careful study of the specimens it would be interesting to see how they compared with stomach washings. The following report is submitted on 293 cases which were bronchoscoped at the Municipal Tuberculosis Sanitarium, Chicago.

The 293 cases represent admissions to the sanitarium or cases referred by its clinics. All cases had chest x-ray evidence of pulmonary disease and were considered to have pulmonary tuberculosis until proved otherwise. This work is a comparison of a single bronchoscopic specimen with all other tests done for isolation of tubercle bacilli, either in the sputum or stomach wash. The bronchoscopy was done for (1) suspect bronchial disease, (2) three or more consecutive negative 24-hour concentrated sputums after admission to the sanitarium and (3) preoperative study. There were no deaths or serious complications. All cases were reviewed six or 12 months later with subsequent tests for tubercle bacilli.

A bronchoscopic specimen could be aspirated in most all cases, although it may have been slight in some and it had to be aspirated with care. The volume of the specimen was never more than 2 or 3 cc and collected in special sterile tubes and sent to the laboratory immediately. A small portion of the specimen was used for a gram stain and acid-fast stain and the balance was used for culture by the usual procedure on modified Tween 80 medium. Growth of the culture was usually present in nine to 30 days at the most, and the growth was faster and more luxuriant than from sputum or stomach wash specimens, apparently due to less contaminants. Positive direct smears of the bronchoscopic specimen for tubercle bacilli were always confirmed by a positive culture. The high percentage of direct positive smears of the bronchoscopic specimen was due to the fact that a skilled technician was in charge of the work. Approximately 200 cases were run before this

series was started, and various types of controls to check the sterility of the instruments, culture methods and smear method were done

Group 1 represents all the cases in which the first and sometimes the only tubercle bacilli were found in the bronchoscopic specimens. Usually, the positive bronchoscopic specimen was confirmed by positive sputum or sputum culture later. Confirmation may take from one to 12 months following the report of the bronchoscopic specimen.

Group 2 represents the few cases in which a diagnosis was made by a positive stomach wash culture and guinea pig confirmation of tubercle bacilli. All sputums and bronchoscopic specimens were negative. Confirmation of the diagnosis was made by observation of the case.

Group 3 represents the cases in which the bronchoscopic specimen failed to confirm a positive sputum. Repeated bronchoscopic specimens with guinea pig inoculation would decrease this percentage.

Groups 4 and 5 represent the positive and negative cases confirmed by bronchoscopic specimens and probably act as the best controls of the procedures.

Stomach washes were not done in all the cases in Group 1 and, therefore, cannot be fairly evaluated. However, the bronchoscopic specimens can be obtained as easily as stomach wash specimens, and the bronchoscopic specimens are much easier to handle and process in the laboratory than either sputums or stomach wash specimens. In general, the bronchoscopic specimen seems to be more dependable than the sputum specimen, both on direct smear and culture for tubercle bacilli and also more dependable and accurate than the stomach wash findings. Bronchoscopic specimens are now being called for by our staff in questionable cases before discharge and where the other laboratory tests for tubercle bacilli fail to coincide with the x-ray and clinical findings.

The work of Holm in Denmark, reveals that sputum cultures of two to 30 colonies of tubercle bacilli are negative on direct smear. Our bronchoscopic specimen cultures often show only two to 12 and 16 colonies after 30 days of growth. This excellent study started by Holm can be carried even further by carefully obtained bronchoscopic specimens and the use of better culture medias and guinea pig inoculations for the determination of tubercle bacilli.

Recent Advances in the Conservative Treatment of the Giant Cavity*

DONATO G. ALARCON, M.D., F.C.C.P.

Mexico City, Mexico

A giant cavity is a huge excavation which involves the greater part of a lobe or a whole lobe. When it occupies more than one lobe, we do not speak of giant cavity but of lung emptying, "vaciamiento pulmonar."

There are two types of giant cavities, and their differentiation is important since the treatment varies with the type. The first is the inflated, hypertensive giant cavity with a check-valve mechanism whose volume depends on the function of this valve. The second is the giant cavity following the progressive destruction of the surrounding tissue. The inflated cavity is not necessarily surrounded by infected lung tissue but can develop in almost healthy tissue, while the destructive cavity is necessarily surrounded by diseased tissue subjected to a more or less rapid process of destruction. While the differentiation between an inflated and a destructive cavity is sometimes easy, it is frequently difficult.

Radiologically, we can say that a cavity is valvular when it appears in tissue little affected by condensation and/or caseation. The volume quickly surpasses that of the initial lesion, its contour is spherical or oval with thin walls. The destructive cavity is also round until it reaches a certain size when it loses this characteristic and is molded by the thoracic wall, the fibrous tissue formation or other hard surrounding tissues. This type of cavity is surrounded by densely condensed tissue, partly diseased and partly compressed, which casts a heavy shadow. Usually this cavity has a slow progress, or it may progress rapidly in caseopneumonic process. It is seldom isolated and seldom corresponds to unilateral disease. On the contrary, bilateral involvement is the rule.

Clinical observations offer different data.

The inflated cavity is usually silent. The destructive cavity, surrounded by solid conductive tissue, gives the typical cavity syndrome, with expiratory cavernous breathing, coarse rales associated with sibilant rales. However, sibilant rales may occasionally be found in inflated cavities.

Radiologically we may observe the expansion of the cavity under

*Presented at the VIII Panamerican Congress of Tuberculosis, Mexico City, Mexico, January 23-29, 1949.

cough strain, with a slow return to its original size This phenomenon is not easily or frequently visualized

In both types, the sputum is usually positive but in the destructive type the number of bacilli is greater for obvious reasons

The technique that we wish to present concerns the treatment

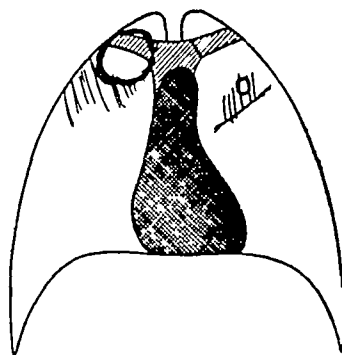
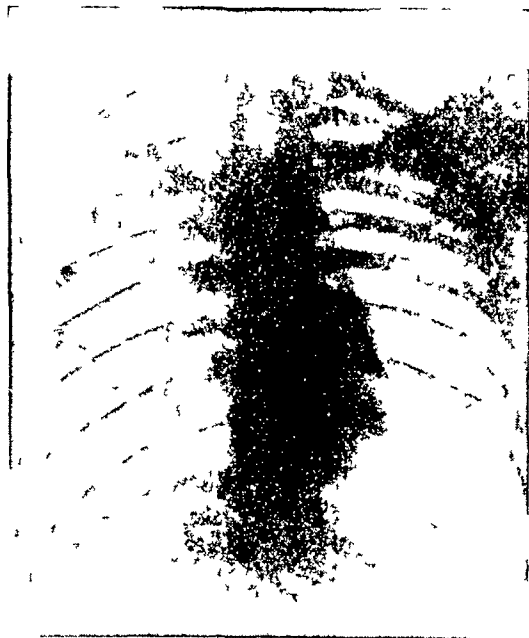


FIGURE 1, G.M. Bilateral caseo-pneumonic lesions Large apical cavity on the right side Its limits are very close to the chest wall Poor indication for the conventional extrapleural pneumothorax On the left, a small cavity is located under the clavicle Tubercle bacilli very numerous in sputum

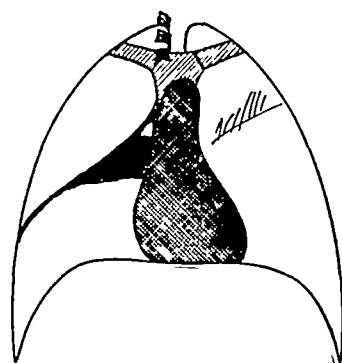


FIGURE 2, G.M. As the pleurae were found adhered, a combination of upper three rib thoracoplasty and extrapleural pneumothorax as described, was done The cavity fell and its size very markedly diminished

of these two types of cavities which constitute one of the greatest difficulties encountered by the thoracic surgeon. These cavities react to pneumothorax in an inconstant and unpredictable manner. Intrapleural pneumothorax is sometimes attempted in spite of the slight chances of success. These attempts are justified by a

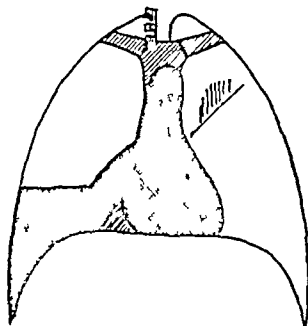


FIGURE 3 G.M. The collapse was considered insufficient and a second stage was performed to enlarge the chamber and closure of the cavity was obtained



FIGURE 4 G.M. Conversion of the extrapleural chamber to oleothorax (mineral oil). The condition became immediately inactive. Sputum and gastric contents persistently negative for over one year. Patient is leading normal life.

rare favorable outcome, provided the pthysiologist will opportunely discontinue an inefficient or incomplete pneumothorax An attempt at pneumothorax is also justified for ascertaining whether the pleura is free, even though it has been decided not to carry out a gaseous collapse A free pleural space will modify the technique that must be followed

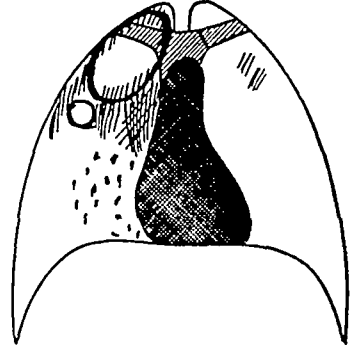


FIGURE 5 ES Giant cavity in the right upper lobe and another smaller one underneath Intrapleural pneumothorax was continued for several years on that side but was abandoned 14 years ago A large nodule is visible under the left clavicle Sputum Tubercle bacilli very numerous

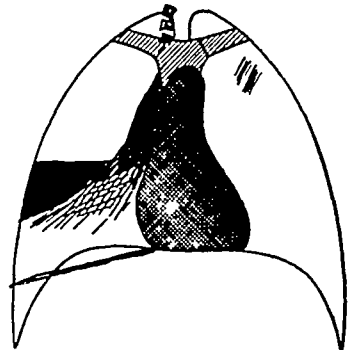


FIGURE 6, ES To avoid thoracoplasty and deformity, the combination thoracoplasty-extrapleural pneumothorax was performed with excellent results The upper lobe seems to be collapsed and the cavity closed and protected from perforation by the soft tissues left on the surface of the lobe

Before any therapeutic decision is carried out, the bronchial patency must be determined by means of needling the cavity. This puncture will indicate if the cavity is hyper- or hypotensive, and thus, if the bronchus is constantly open or not. The changes in intracavitary pressure may be observed after coughing as air enters the bronchus and the time necessary for its return to the

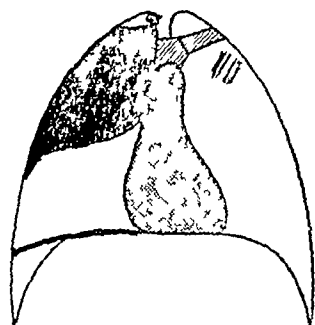


FIGURE 7 ES Conversion to oleothorax with 1000 cc. Nujol when the chamber was filled up

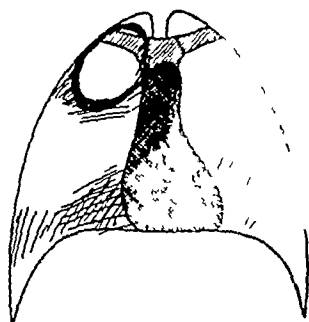


FIGURE 8 EM Giant cavity in the right upper lobe and exudative spread over the lower lobe and the opposite lower lobe. Sputum very large number of tubercle bacilli

initial pressure is noted This procedure should be carried out only when pleural synechia is present at least within the area of the thoracocentesis

Besides intrapleural pneumothorax which is frequently inefficient in the treatment of these cavities, we have other conservative and radical recourses The conservative methods are Monaldi's

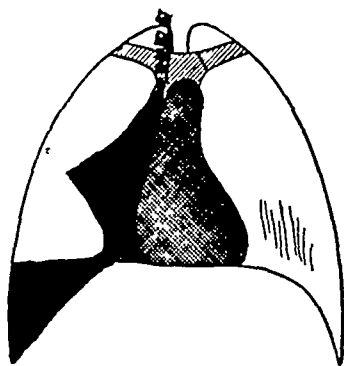


FIGURE 9, E M Large extra-pleural chamber is obtained after the combination of thoracoplasty - extrapleural pneumothorax is done

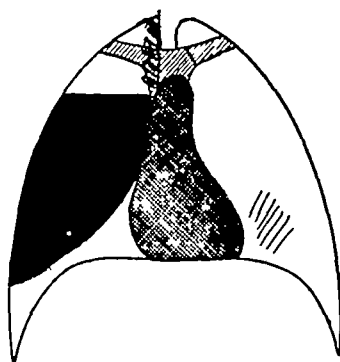


FIGURE 10 E M Conversion to oleothorax to make a permanent collapse Sputum and gastric contents repeatedly negative

intracavitary aspiration, extrapleural pneumothorax, and other nondeforming extrapleural operations. The radical procedures are extensive thoracoplasty and pulmonary resection.

Thoracoplasty and resection are both disfiguring because pneumonectomy and lobectomy in tuberculosis must be followed by thoracoplasty. Especially in lesions that are rarely unilateral, thoracoplasty before or after pulmonary resection must be carried out if we do not wish to provoke flare-ups in the remaining lung.

We advocate the treatment of giant cavities by conservative methods for several reasons:

- 1) Usually the patients are young and their future is affected by great disfigurements such as that caused by an extensive thoracoplasty as must be done in these cases.

- 2) The most extensive thoracoplasty may fail to collapse a giant cavity and may only result in an incomplete closure.

- 3) Pulmonary resection has a greater operative risk in bilateral cases.

Extrapleural methods are preferable to those like the Monaldi method because we consider that eventually, as in most cases of giant cavity, these methods lead to a complementary thoracoplasty. However, we admit that in some expert hands the Monaldi intervention is efficient in an unexpected manner.

With reference to extrapleural pneumothorax, we have already published several works which try to justify the use of this method by presenting examples of the good results. It is particularly indicated in the inflated cavity where there is a thick layer of healthy tissue between the cavity and the thoracic wall allowing a separation far from the cavity.

We do not recommend extrapleural pneumothorax for cavities of the destructive type so huge that they seem to be limited in size by the thoracic wall, because of the great risk of provoking an early or late perforation with subsequent empyema. This type of cavity contraindicates conventional extrapleural pneumothorax. That is why our efforts have been directed towards evolving a technique which will avoid the aforementioned disadvantages but offer reasonable hopes for the closure of the cavity.

The standard extrapleural thoracoplasty with a more or less extensive rib resection but without apicolysis does not solve the problem in the majority of cases. Semb's thoracoplasty more frequently solves this problem though not always, and leaves great disfigurements because of the extensive resections needed in two or three stages. Sometimes, after all these steps, we find that the cavity has not closed but eludes collapse by just descending and decreasing in size. Then secondary pneumonectomy is justified.

However, both thoracoplasty and this latter operation deform

the thorax and we do not believe this is justified if there is a conservative method which, without deformity, and in one or two stages, will accomplish the same or even better results than an extensive thoracoplasty

In order to avoid the disadvantages of extrapleural pneumothorax and thoracoplasty, we have combined the two operations with the following advantages

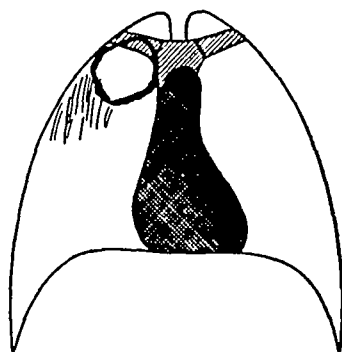


FIGURE 11 A.M Large apical cavity on the upper lobe
Pleural synechia

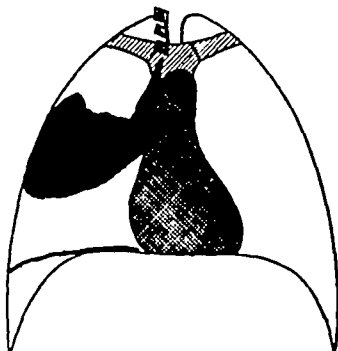


FIGURE 12, A.M The combination thoracoplasty - extrapleural pneumothorax was done

- a) A collapse equally extensive or more so than that obtained by thoracoplasty
- b) There is no appreciable disfigurement even in the naked thorax
- c) The lung is protected, so that this type of cavity is not liable to rupture as in the usual extrapleural pneumothorax
- d) It is a permanent procedure like thoracoplasty

*Technique for Extrapleural Pneumo-Oleo thorax
Combined with Apical Thoracoplasty*

This is a preliminary report of our treatment of giant cavities by this technique. To-date our results have been very satisfactory.

The operation is carried out with endotracheal ether-cyclopropane anesthesia, with frequent aspirations. The incision is the usual for a thoracoplasty, that is, the paravertebral incision including skin and muscles. The first steps of the procedure are performed like a three rib thoracoplasty, resecting almost all of the third rib and all of the first and second ribs in the order mentioned. This resection is intraperiosteal, the periosteum is left "in situ." We wish to emphasize that in this operation it is not necessary to resect the transverse process or to disarticulate the ribs.

From this step forward the operation is carried out as in Semb's thoracoplasty, differing from this author's technique in a few details that are important. First, we try to conserve all the soft

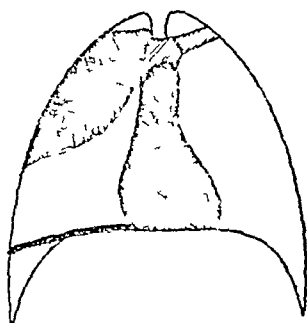


FIGURE 13 A.M. Conversion to oleothorax. Sputum and gastric lavage negative

tissues that cover the lung anteriorly, laterally and posteriorly, so that we maintain the adhesion of the periosteum, intercostal muscles, blood vessels and nerves to the parietal pleura. It is through this adhesion that we try to protect the cavity wall.

Then the lung is separated by blunt dissection on its mediastinal aspect down to the hilum, with extreme care because of the danger of injuring blood vessels, nerves, lymph nodes and the thoracic duct. Then the muscles, intercostal vessels and nerves are cut after ligation, the section is done as far anteriorly as possible as well as posteriorly. Thus the lung stump falls vertically and a first stage of Semb's thoracoplasty has been carried out with slight variations, but now instead of limiting ourselves to the separation and descent of the apex, we also make an extrapleural decollation as low as is anatomically possible, leaving a subtotal extrapleural space. Sometimes we leave a drainage at the lowest point, depending on the hemorrhage, and suture in two layers.

The operation is well tolerated and we attribute this to the anti-shock treatment of the present day, including generous transfusions. Twenty-four hours later we withdraw the drainage tube and occlude the course of it. The extrapleural pneumothorax is maintained in the usual manner and approximately one month later we convert it to oleothorax.

The examples presented show that a greater collapse is obtained than in thoracoplasty or even in Semb's operation. We have found, in our limited experience, that the soft tissues protect the cavity from perforation and our experience for over 10 years with mineral oil in extrapleural pneumothorax has shown us it is well tolerated.

The aim of this procedure is to obtain a permanent collapse in one operation. Sometimes we reoperate if the collapse is insufficient. This brings no further disadvantages since there is no disfigurement of the thorax. This operation must not be confused with similar procedures in which costal resection is carried out including the periosteum and intercostal vessels, since, on the contrary, owing to the sparing of these tissues we have obtained satisfactory results.

RESUMEN

Las cavernas gigantes pueden dividirse en dos grupos, las infladas con poca destrucción tisular y las destructivas con pérdida de tejido muy considerable, limitándose a veces aparentemente por la pared torácica.

Estas cavernas son difíciles de ocluir por los recursos de colapso habituales y cuando se logra es a costa de grandes deformaciones que afectan el futuro de los sujetos jóvenes.

La toracoplastia sea desde luego o después de neumonectomía es la intervención obligada

A fin de evitar las operaciones deformantes el autor presenta una técnica quirúrgica consistente en una combinación de toracoplastia apical de tres costillas a la manera de Semb con modificaciones pequeñas, con un neumotórax extrapleurar desde la cuarta costilla hasta el surco costo diafragmatico Toda la operación se realiza en un tiempo o en dos cuando más

Después de un mes el extrapleurar combinado se convierte en oleotórax con el fin de obtener un colapso permanente

El aceite mineral es bien tolerado segun su experiencia en oleo extrapleurar que sobrepasa diez años

Las ventajas que presenta el procedimiento son las siguientes

a) Realiza un colapso tan extenso o más que el de una gran toracoplastia

b) No ocasiona deformación del tórax en forma apreciable ni aun en el tórax desnudo

c) No expone a perforación de la caverna y empiema consecutivo como el extrapleurar corriente si se aplica a caverna gigante

d) Es un método permanente como la toracoplastia

e) Puede habitualmente realizarse en un tiempo

Presenta algunos ejemplos de esta técnica

Surgery in Congenital Heart Disease*

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Woodbury, Tennessee

Introduction

The large subject of congenital heart disease may be submitted to an over-simplified and incomplete but practical subdivision into a cyanotic and a non-cyanotic group. The cyanotic group includes tetralogy of Fallot, truncus arteriosus and cor triloculare, while in the non-cyanotic group are found patent ductus arteriosus and coarctation of the aorta. The cyanotic group may be further subdivided into those cases characterized by inadequate oxygenation in the lung, and those with reduced flow of blood to the lung. Of those with reduced pulmonary flow, tetralogy of Fallot, cor triloculare and truncus arteriosus are amenable to indirect surgical relief. The tetralogy with the Eisenmenger complex, transposition of the great vessels, and aortic atresia have not as yet successfully been submitted to surgery.

The fact that certain types may be greatly benefitted by surgical therapy has required effort to make an accurate diagnosis and estimate prognosis, to obtain help in deciding what type of operation to do, and to establish criteria for objective evaluation of the results. These needs are responsible for the reinvestigation and application of many old well-known physiologic facts, and the development of some new procedures for study.

Patent Ductus Arteriosus

The first form of congenital heart disease to be attacked surgically was patent ductus arteriosus. The high incidence of bacterial endocarditis, the frequent disability and the short life expectancy led Strieder first to attempt ligation of the persistent patent ductus. Unfortunately, his patient died and to Gross goes credit for the first successful ligation, and to his medical colleague Hubbard goes commendation for the courage to recommend and allow this then unproved operation to be performed on his patient. Because some of the cases have recanalized or a patent canal has persisted, Gross proposed and has practiced division of the ductus in most of his cases. Infected cases of subacute bacterial endocarditis have become infection-free following the operation, and the majority done have shown great functional improvement.

*Presented at the 6th Annual Meeting of the Southern Chapter, American College of Chest Physicians, Miami, Florida, October 25, 1948

The diagnosis of patent ductus arteriosus usually is easy to make. The patient may appear pale or thin, and sometimes slightly cyanotic. In other cases there is an accentuated ruddiness of complexion. The heart is somewhat enlarged and there is a machinery or to and fro murmur loudest over the pulmonic area. The pulmonary conus (Fig 1) is very prominent and fluoroscopically there is a "hilar dance" and pulmonary congestion. In other cases the possibility of associated anomalies like intracardiac septal defect, or absence of the pulmonary artery must be considered. For this purpose the cardiac catheter (Figs 2A and 2B), developed by Cournand and associates, has proved useful in obtaining intracardiac pressure readings and samples for blood gas analysis.

The problems of diagnosis and treatment in patent ductus arteriosus may be illustrated by a case example (L T). A child of 10, poorly developed, pasty of appearance and slightly cyanotic had disabling dyspnea on exertion. His condition in the past year had grown steadily worse and it was the consensus that he would shortly die. A cardiostethogram (Fig 3) portrays graphically the machinery murmur. Because of the very loud systolic

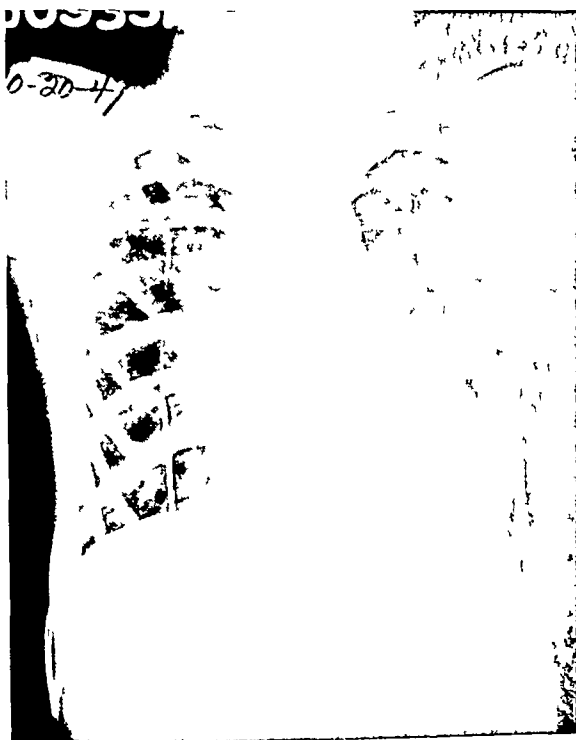


FIGURE 1 Patent ductus arteriosus

murmur, an intracardiac septal defect was also suspected. The known large size of the ductus and a wide pulse pressure of 120/50 aroused fear that the ductus might be providing the principal pulmonary flow. Therefore, catheterization of the right heart was done. The blood gas determinations from the catheter sample are shown in Table 1.

TABLE 1
Heart Catheterization Study (L T 10/1/47)
Findings from blood gas analysis in patent ductus arteriosus

	O ₂ Content	Per cent Saturation	Pressure MM Hg
Right Ventricle	12.75 V/%	69.9	25
Right Auricle	12.75 V/%	69.9	10.7
Superior Vena Cava			1.5
Femoral Artery	17.54 V/%	96.3	110/30
O ₂ Capacity	18.25 V/%	RBC 4.5 M	Hgb 13.4 G

These prove that there is no intracardiac shunt, there is inflow and outflow to the right ventricle, the amount of outflow is normal, since the right ventricular pressure is within normal limits, and the right auricular pressure is not increased (absence of venous stasis). Final and confirmatory proof of demonstrated higher pressure in the pulmonary artery than in the right ventricle

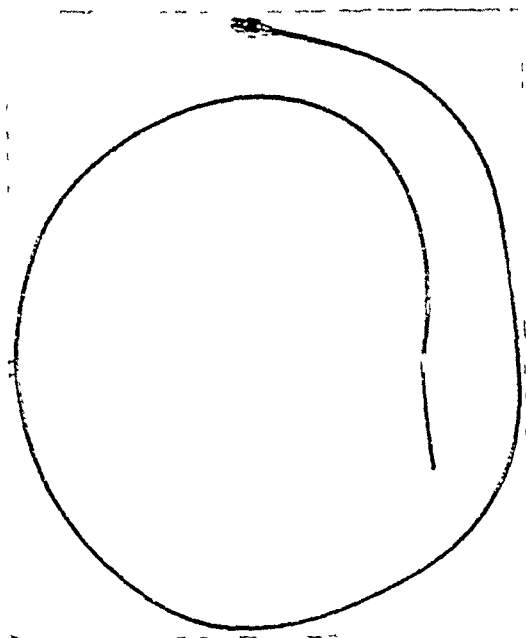


FIGURE 2A Cournand cardiac catheter

could not be obtained because the catheter could not be successfully passed into the pulmonary artery. The basal metabolism was elevated at plus 30, and the oxygen consumption was 170 cc per minute, indicative of increased oxygen usage.

From these data the cardiac output and pulmonary flow were calculated according to the Fick principle (Table 2 and Table 3). The pulmonary net shunt amounted to 20 cc per minute. Therefore, from these studies we were justified in concluding that the child had patent ductus arteriosus, and that he did not have any other cardiac anomaly.

TABLE 2

The Fick Principle (Cardiac Output)

1 Total Output (cc's/min) =

$$\frac{O_2 \text{ Consumed in cc's/min}}{O_2 \text{ Cont Art B Vol \%} - O_2 \text{ Cont Mix Ven B Vol \%}} \times 100$$

2 Systemic Flow (cc's/min) =

$$\frac{O_2 \text{ Consumed in cc's/min}}{O_2 \text{ Cont Art B Vol \%} - O_2 \text{ Cont R Aur B Vol \%}} \times 100$$

TABLE 3

Heart Catheterization Study (J H 10/14/47)

	O Content	Per cent Saturation	Pressure MM Hg
Right Ventricle	6.29 V/%	61	32
Right Auricle	3.74 V/%	33.5	
Femoral Artery	5.5 V/%	53	130.50
O ₂ Capacity	10.4 V/%	RBC 4,810,000	Hgb 7.6 G



FIGURE 2B Catheter in right heart chambers

The ductus was ligated and the child is much improved, and is able to lead a normal life. It was not divided, although such is our preference, because of the critical nature of his illness and the likelihood that he would not survive the operative procedure. This is the only ligation we have done. Our other cases have been treated, after the method of Gross, by division. Postoperatively the basal metabolism was reduced and the pulmonary conus became smaller. We have closed the ductus in three cases by division and in 1 by ligation. In a fifth case, the ductus spontaneously ruptured on the anterior wall with fatal hemorrhage as it was being exposed, and before any sutures or clamps had been applied.

Coarctation of the Aorta

Coarctation of the aorta, another of the non-cyanotic types of heart disease, is recognized by a high blood pressure in the upper extremities, a very low or absent blood pressure and absence of pulsations in the lower extremities and notching of the ribs by x-ray examination. The notching is caused by pulsations of enlarged collateral vessels against the ribs. In the diagnosis of this disease one is faced with an outflow problem, in contrast to most forms of congenital heart disease, in which the diagnosis is largely on the basis of inflow data. Angiocardiography is a method of

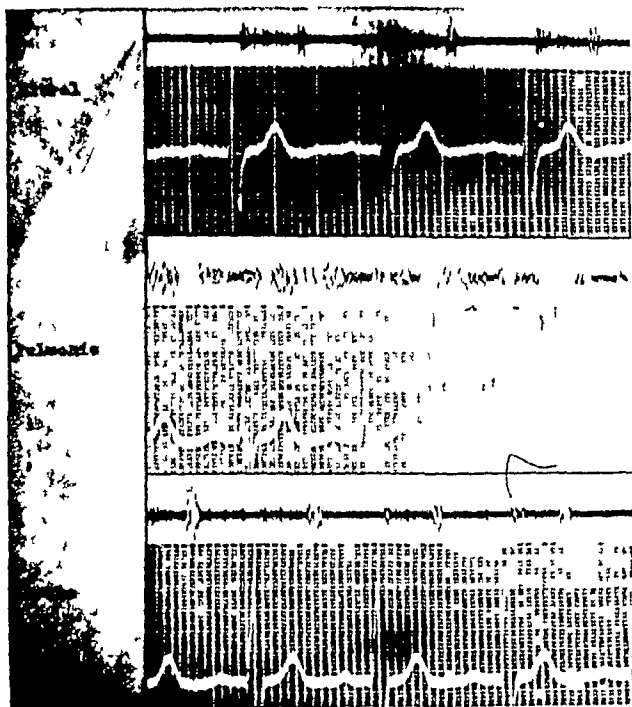


FIGURE 3 Cardiostethogram in patent ductus arteriosus

determining cardiac outflow characteristics and is interesting but not usually necessary for diagnosis. Two operative procedures may be employed for the relief of coarctation. One is by means of a shunt around the stricture, which is usually located in the aortic arch just below the subclavian origin. This consists in the anastomosis of the greatly enlarged left subclavian artery to the diminutive aorta distal to the shunt. The other procedure, proposed by Crafoord, is resection of the stricture and end to end anastomosis to the aorta. Bradshaw has developed an ingenious clamp (Fig 4) for occluding the aortic blood flow during the period of anastomosis. The accompanying photograph shows an aortic stricture which was excised (Fig 5) with end to end anastomosis. Although the anatomic and circulatory results were good, the hind quarters suffered motor paralysis which we fear will be permanent.

Tetralogy of Fallot

Uncounted numbers of anatomists, from Galen forward, established the normal anatomy of the heart and the primary vessels. The great Maude Abbott, by her lifetime of observation, collection, recording and writing, did more than any other person perhaps, to classify and clarify the pathologic anatomy of congenital heart disease. Fick, Haldane, Carpenter, Van Slyke, A. V. Hill, and many others in the past century developed principles and procedures by which blood flow, pulmonary ventilation and blood gas components may be measured or established with reasonable accuracy. Cournand introduced the cardiac catheter which permits the direct analysis of pressures and blood samples obtained from the right side of the heart, and which has signif-

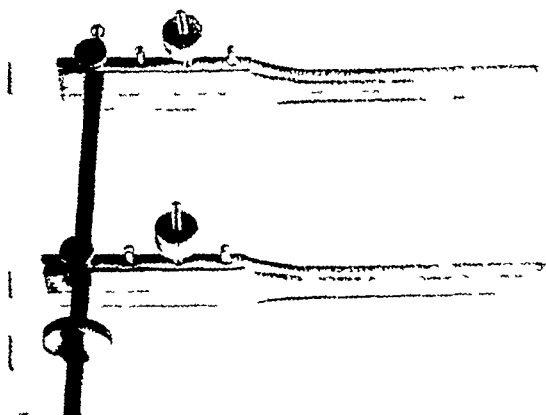


FIGURE 4 Bradshaw aorta clamp

icantly extended the usefulness of physiologic methods of previously mentioned workers

The brilliant American scientist, Alfred Blalock, and the astute clinician, Helen Taussig, in 1945, on the basis of these many preceding contributions, made available a surgical procedure for the relief of certain types of congenital heart disease with cyanosis. They reasoned that the essential fault in tetralogy of Fallot is deficient blood flow through the pulmonary circulation. The Blalock-Taussig operation is designed to increase the flow through the lungs by diverting a portion of the systemic circulation into the lungs by means of an anastomosis between the innominate or subclavian and pulmonary arteries. In other words, an artificial patent ductus is made.

Tetralogy of Fallot is a form of congenital heart disease caused by overriding or dextroposition of the aorta, in which the aorta arises lower than normally from the left ventricle and over the right ventricle. Because of the abnormal origin, the aortic septum can not meet the ventricular septum and a high interventricular septal defect results. There is stenosis of the pulmonary orifice,

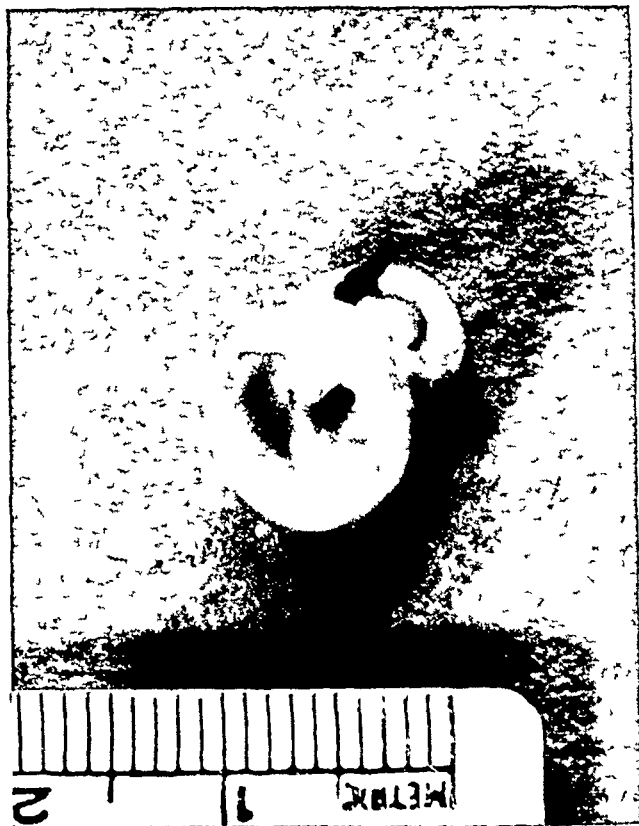


FIGURE 5 Coarctation of aorta specimen

which often extends out onto the pulmonary conus, and accounts for the concavity at the base of the left heart border so often seen by x-ray examination in such cases. The difficulty of getting blood out of the right ventricle causes elevation of pressure and right ventricular hypertrophy, and right axis deviation by electrocardiographic observation. The features of tetralogy of Fallot then are overriding of the aorta, pulmonary stenosis, an inter-ventricular septal defect, and right ventricular hypertrophy.

The signs of tetralogy of Fallot are cyanosis, clubbing, usually a systolic murmur along the left sternal border, but not necessarily a diastolic murmur. Some hearts are very large, others are not enlarged at all. The child as a rule is poorly developed and nourished. Some older children are mentally retarded as a result of chronic anoxemia. If markedly cyanotic, they are extremely dyspneic on even slight exertion. Venous congestion is frequently observed in the upper extremities, on the bridge of the nose, and in the arms. Fluoroscopically, there are no hilar or pulmonary pulsations visible, and instead of a pulmonary conus convexity there is a concavity. This is also known as a pulmonary window. The x-ray picture in the left anterior oblique position is that of a rounded or blunt heart with a narrow aorta and a clear area posteriorly. The right ventricle is enlarged. By electrocardiographic studies, right axis deviation usually is found. The peripheral oxygen saturation is low. The aortic knob is variable in position, sometimes curving to the right and sometimes to the left. The



A B
FIGURE 6A Tetralogy of Fallot in failure
6B Same before failure

position of the aortic arch must be determined and may be done by fluoroscopy with barium to show the position of the esophageal indentation as it passes behind the aorta. The chest, both by physical examination and by x-ray examination is often found to be barrel-shaped from hyperpulmonary ventilation. A typical posture of such children is a squatting position and they are referred to colloquially as "squatters."

Tetralogy cases with deteriorating condition and who are not eating, may become less cyanotic and the red count drop 2 or 3 million. This is no doubt caused by anemia of malnutrition and is a grave sign. In such cases one may expect the heart to enlarge. The massive enlargement that can occur is shown in the two following comparative slides of a child failing rapidly (Figs 6A and 6B). In the figures shown from catheter study, note the anemia as well as severe oxygen unsaturation (Table 4).

TABLE 4

The Fick Principle

Findings from blood gas analysis in tetralogy of Fallot
Case in heart failure from malnutrition

3 Pulmonary A Flow (cc's/min) =

$$\frac{\text{O}_2 \text{ Consumed in cc's/min}}{\text{O}_2 \text{ Cont P V Vol \%} - \text{O}_2 \text{ Cont P A Vol \%}} \times 100$$

4 $\text{O}_2 \text{ Content P V (Vol \%)} = \% \text{O}_2 \text{ Sat P V} \times \text{O}_2 \text{ Capacity Vol \%}$

Assumption—P V Blood is 95% Saturated

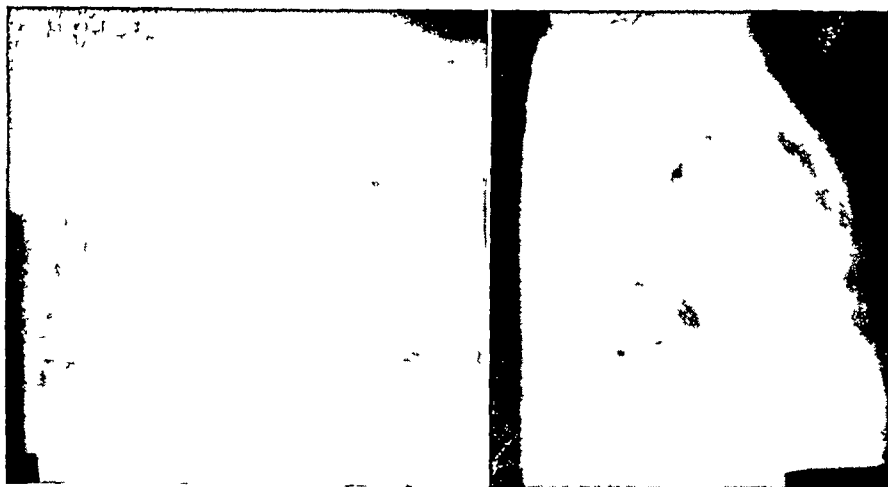


FIGURE 7 Pulmonic stenosis

It is not the cyanosis that is harmful in congenital heart disease, but the peripheral anoxemia which causes it and the compensatory polycythemia. The blood returning from the lungs by way of the pulmonary vein in the majority of heart cases is fully or 95 per cent saturated. This has been confirmed by indirect colorimetry, by calculations according to the Fick principle, and by a few successful catheterizations of the pulmonary vein through an open septum in cases that were deeply cyanotic. These cases provide the only purely objective proof that the theory of Blalock and Taussig is correct in stating that the essential defect is deficiency of blood flow rather than deficiency of oxygenation of the blood that is able to reach the lungs.

There are three principal types of congenital heart disease with cyanosis. Tetralogy of Fallot comprises perhaps 75 per cent of these, in which the cyanosis is dependent largely upon the size of the right-to-left shunt, and the pulmonary stenosis (Fig 7). In cor triloculare, there is a common ventricle with or without a rudimentary outlet chamber. The cyanosis is deep or slight, depending on whether the outlet vessel to the lung is large or small. In truncus arteriosus, cyanosis is slight or absent if the pulmonary artery arises off the aorta. It is intense if the pulmonary circulation is limited to flow through the bronchial arteries. The pulmonary stenosis patient may not be cyanotic at first, but become so later as the patent ductus shuts off, thereby decreasing the blood flow into the lungs. Theoretically, one can use oxygen intravenously to supplant that absorbed by the lungs. However, the amount that can be administered is limited to that which

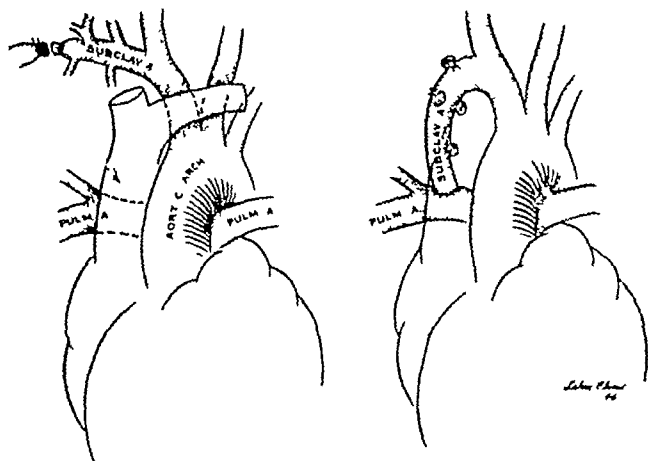


FIGURE 8 Subclavian to pulmonary artery anastomosis—Diagram

will go into chemical solution in the blood, and is only about 1 per cent. We have used this method in one case that became seriously cyanotic during operation. The patient died 9 days later of a cerebral thrombosis, and may have had air embolism through the septum as well.

The purpose of the corrective operation (Fig 8) is to compensate for an adequate flow of blood to the lung. Blalock has advised that one enter the thorax for operation on the side opposite that of the aortic arch, because of the more favorable curvature that the subclavian artery will assume off the innominate as compared to the aortic arch. We have found the left subclavian off a left arch quite satisfactory in 4 cases in which it was used. Either the subclavian or innominate artery is sutured by its end into the side of the pulmonary artery. The use of the subclavian does not seriously endanger the viability of the arm, although a dorsal sympathectomy at the same time is wise in older patients. The sacrifice of the innominate artery dangerously jeopardizes the blood supply to the brain, and significantly increases the mortality of the procedure. Before doing the operation, one should temporarily occlude the pulmonary artery to make certain that its occlusion will be tolerated. It is also wise to measure the intra-pulmonary arterial mean pressure, as pressures above 300 mm of saline indicate that there is probably sufficient blood entering the pulmonary artery. Likewise, the artery should be released slowly after the anastomosis to avoid severe changes in blood pressure and acute pulmonary edema. If a large amount of collateral circulation is found on opening the thorax, it suggests pul-

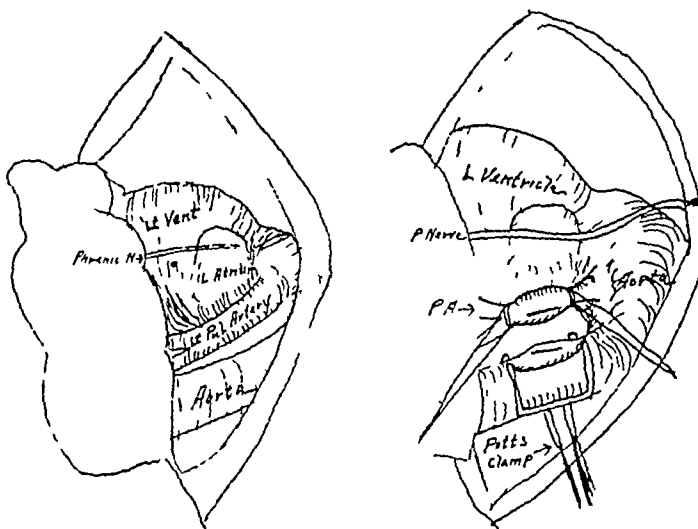


FIGURE 9 Aorta to pulmonary artery anastomosis—Diagram

monary atresia The lung should be reinflated very gradually in these cases lest the pulmonary alveoli be ruptured and artificial pneumothorax be caused bilaterally The heart may increase in size postoperatively, but most of the increase is limited to the first three weeks We have not used heparin and dicumarol either pre- or postoperatively Blood-letting preoperatively to reduce viscosity has been tried, but caused a physiologic crisis and the blood had to be replaced The disadvantage of the subclavian artery anastomosis is the small caliber of the vessel There is danger that the opening may thrombose from polycythemia I have already mentioned the disadvantages of the innominate anastomosis

To overcome some of these disadvantages and to make the operation available to very small children, Potts has carried out a direct anastomosis of the aorta to the pulmonary artery (Fig 9) The photograph shows the clamp (Fig 10) that is used to occlude one wall of the aorta and still allow blood to pass through to the lower extremities during the procedure An anastomosis about 8 to 9 mm in length is made with very fine silk This is another method of constructing an artificial ductus and here in diagrammatic form is the way the operation is done We have encountered no technical difficulty in the use of this method in 4 cases, and have achieved a most satisfactory result in 2 cases Each of the other two children died of progressive hemorrhagic pulmonary edema about 24 hours afterward At autopsy in each the anastomosis was found intact In one the anastomosis was thought to be too large, in the other there was but a single ventricle We have had one death in 5 cases of subclavian pulmonary anastomosis This occurred from cerebral thrombosis in a woman of



FIGURE 10 Smith-Potts aorta clamp

27 years with a red count of 9 million and we believe that she may have been too old for the operation

CONCLUSION

In conclusion, I would emphasize that the Blalock-Taussig and Potts operations are of value only in cyanotic cases caused by deficient blood flow. The optimum age for the operation is probably from 5 to 9 years, although children as young as a few months and adults in the thirties have been done. One must remember that, in vascular surgery terms, the vessels are three times the chronological age, that is, an operation on the aorta of a person of twenty-five carries the operative risk that a gastrectomy or pneumonectomy or similar major procedure would carry in a person of seventy-five.

This is a field in which the disease is fascinating; the methods of diagnosis tedious, time-consuming and often expensive. Most of the patients apparently are impoverished. The operation is difficult, but stimulating. The successes are far from uniform but steadily improving. However, I know of nothing more gratifying to a surgeon than the feeling that his efforts may have contributed in altering the hopeless outlook of some of these little children to that of a functionally normal childhood.

CONCLUSION

Como conclusión desearia insistir en que las operaciones de Blalock-Taussig y Potts son de valor solamente en los casos cianóticos causados por deficiente corriente sanguínea. La edad óptima para la operación es probablemente de los 5 a los 9 años, aunque niños de algunos meses o adultos alrededor de los treinta años han sido operados. Debe uno recordar que por lo que se refiere a la cirugía vascular, los vasos son tres veces mayores que su edad cronológica, esto quiere decir que una operación en la aorta de una persona de 25 años, lleva consigo el riesgo de una gastrectomía o una neumonectomía u otro procedimiento similar en una persona de 75 años.

Este es un campo en el que la enfermedad es fascinante, los métodos de diagnóstico tediosos, prolongados y costosos. La mayoría de los enfermos están aparentemente empobrecidos. La operación es difícil pero estimulante. Los éxitos están lejos de ser uniformes pero constantemente mejorando. Sin embargo, no conozco nada más halagador para un cirujano, que la sensación de que sus esfuerzos pueden contribuir para alterar el desesperado futuro de algunos de estos niños trayéndolos a una infancia funcionalmente normal.

D I S C U S S I O N

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Dr Adams showed you a picture of the Bradshaw clamp which is indeed a valuable adjunct to coarctation operation. There is one precaution I suggest that you take before attempting to use it and that is that you either wrap the arms of the clamp with umbilical tape or slip a little tube of stockinet or something over it. We were much interested to watch the effect of the aortic pressure against the proximal bar of that clamp, and it was with some consternation that we noticed a gradual migration of that bar toward the line of incision. In our particular case we had plenty of length, it was an easy case to do and it gave us no trouble but I could easily see how working with a narrow margin and with no extra friction between the clamp and the aorta, it could easily slide itself off, because you can't hold an aorta tight shut with your fingers for any length of time. The pressure there is something terrific

A Modern Evaluation of Extrapleural Pneumonolysis in the Treatment of Pulmonary Tuberculosis with Special Reference to Methyl Methacrylate "Plombage"

Review of 26 Cases*

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The term "extrapleural pneumonolysis" implies a freeing of the lung by the establishment of a cleavage plane between the parietal pleura and the endothoracic fascia in order to obtain an effective, as well as a selective collapse of an area of circumscribed tuberculosis in the apex of the lung. As a result of such a pleurolysis an extrapleural space is created which demands the insertion of some extraneous material for maintenance of the pulmonary collapse so produced.

It was the search for an optimum "filling" material that made this type of pneumonolysis one of the most interesting of all thoracic surgical procedures. In reviewing the literature one finds that this procedure waxed and waned in popularity since its introduction into the surgical literature by Tuffier in 1891, each decade introducing new "plombe" materials which, at the time of their introduction, were thought to represent the ideal extraneous material for maintenance of the extrapleural space. However, in each case the new burst of enthusiasm was short-lived and the popularity of the procedure would decline until the introduction of a new "plombe" material would lead to its revival.

In the spring of 1946 Wilson¹ presented his experimental work on methyl methacrylate (lucite) and first suggested its use as an extrapleural filling material. We accepted this idea with eagerness and after reviewing the literature and obtaining some lucite balls, performed our first extrapleural pneumonolysis with lucite pack in September of that same year. Our institution houses 1,000 tuberculous patients and the surgical unit at Oteen performs the thoracic surgical procedures for an adjoining hospital that houses some 500 patients with tuberculous disease. This makes 1,500

*From the Department of Medicine and Surgery, Veterans Administration, Oteen, North Carolina, published with permission of the Chief Medical Officer, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

tuberculous patients from whom to select optimum cases for performance of this collapse procedure. It was from this number that the 26 patients receiving extrapleural pneumonolysis with lucite pack were selected. Each case was carefully studied with strict adherence to the indications established by surgeons who had reported earlier series of cases using such packing materials as paraffin, muscle graft, etc.

This paper is not being written in an effort to praise the procedure or to establish methyl methacrylate as the optimum filling material for the extrapleural space. We feel that our results show, unequivocally, that extrapleural pneumonolysis with lucite pack has but a narrow range of usefulness in the surgery of pulmonary tuberculosis, and that methyl methacrylate, although one of the best "plombe" materials introduced into the surgical field, is not divorced from the usual complications arising concomitant with the introduction of a foreign substance into the tissues of the human body. We would also like to place a word of warning for the enthusiastic novice experimenting with this type of procedure so that he will not use this operation injudiciously and with irretrievable violation of the indications for its use formulated over the past half century. The indications for an operation that has been tried by the world's foremost thoracic surgeons should not be changed on short notice because of the introduction of what only promises to be the long sought "optimum" extrapleural filling material.

In performing this operation we should select only those cases which offer reasonable assurance that some benefit may ensue from this collapse procedure and concentrate our efforts on these cases rather than on those that offer no reasonable hope of cure. To evaluate a new surgical procedure or a new modification of a preexisting established surgical procedure, one should select trial cases most judiciously so that a true evaluation can be made early in its evolution and thus prevent acrimonious criticism of the procedure before it has received a fair trial.

Indications

Tabulated below are a few of the indications for extrapleural pneumonolysis during the time when this procedure was being employed on our surgical service. Each indication is briefly discussed.

- 1) Apical cavities of small dimensions
- 2) Inadequate respiratory reserve
- 3) Bilateral disease
- 4) Residual cavities under thoracoplastic collapse

5) Extrapulmonary complications where the age and general condition of the patient contraindicate thoracoplasty

When the internist informs us that he has a case for extrapleural pneumonolysis, we assume that the patient has a small apical cavity with dimensions of four centimeters or less, located at or above the level of the first anterior interspace. This cavity may be thick-walled, as proposed by Winternitz,² provided a large area of parenchymal induration does not surround it. On the other hand, it may be thin-walled, as proposed by the majority of workers in this field, provided its proximity to the parietal pleura does not make extrapleural dissection hazardous and provided no evidence of "blocked" or "tension" cavity exists.

With reference to inadequate respiratory reserve, it is an established fact that this procedure produces a selective collapse with the maximum preservation of normal pulmonary parenchyma and respiratory function, and in patients who have failed to respond to simpler collapse measures extrapleural pneumonolysis with plombage may offer them their only chance of cure. In many cases the respiratory reserve is increased following this procedure, a fact explained on the basis of better utilization of the inspired air following compression of a diseased segment of lung. This does not mean that every patient demonstrating a low vital capacity should be a candidate for the lucite operation, nor does it mean that we can promise the patient a cure even if his lesion is optimum for the procedure. It merely means that in a few selected cases the operation may be employed in an effort to close a small apical cavity. It is taken for granted that the patient is a good risk and that there is a chance for improvement or ultimate cure if the operation achieves its objective—closure of the cavity.

In bilateral pulmonary disease extrapleural pneumonolysis again finds a field of usefulness. In many instances a small apical lesion on one side can be closed by this procedure allowing a thoracoplasty on the contralateral side of greater involvement and indication. Of course, in these cases we must have an optimum apical lesion for the extrapleural procedure and our indications should not be altered because of the bilateral nature of the disease. Also this operation should not be employed if the lesser lesion can be controlled by one of our simple collapse measures.

In cases in which residual cavitation persists under an area of thoracoplastic collapse, our staff agrees with Dolley³ who states

" in thoracoplasty we plan to carry on to cavity closure, not cavity wall approximation. It is very firmly our opinion that, unless cavity walls are actually brought together, healing does not take place."

Therefore, one might well assume that if a residual cavity is demonstrable in the first postoperative roentgenograms following the final stage of thoracoplasty, some type of supplemental operation will be necessary in order to close it. Although our results as tabulated in Table I show a high percentage of cavity closures (75 per cent) in this type of case, our department feels that lucite pneumonolysis is too hazardous a procedure to be used in these post-thoracoplasty cases. Since our experience with lucite pack for closure of such residual cavities, we have used the Eloesser⁴ type of open cavernostomy and find that our results are much better with this latter procedure. Also, with the advent of streptomycin, we have been using lobectomy and pneumonectomy in selected cases, and again a far superior operation is at our disposal for such cases.

Whenever extrapulmonary complications or the age and general condition of the patient contraindicate thoracoplasty, extrapleural pneumonolysis with lucite pack may be employed to great advantage. Again, this operation should be used only in those lesions that offer a reasonable chance of closure. The advantage of lucite pneumonolysis in these poor-risk patients is that it can be performed in one stage, under local anesthesia, under which circumstances it is a relatively non-shocking operation. The additional factor of its selectivity with maximum preservation of non-diseased pulmonary parenchyma and its minimal interference with the normal expectoration mechanism make its use optimum in this type of patient.

Operative Technique

Both the anterior and posterior incisions have been employed in our series of cases. However, we prefer the posterior approach.

TABLE I—Results in
22 Successfully Performed Extrapleural Pneumonolyses with Lucite Pack

Type of Pack	Patients	— C A V I T Y —		— S P U T U M —		Cases Negative Before and After Operation	Sputum Conversions
		Closed	Unclosed	Positive	Negative		
Primary	14	6 (42.9%)	8 (57.1%)	9 (64.3%)	5 (35.7%)	0	5 (35.7%)
Secondary	8	6 (75.0%)	2 (25.0%)	3 (37.5%)	5 (62.5%)	4 (50.0%)	1 (12.5%)
TOTAL	22	12 (54.5%)	10 (45.5%)	12 (54.5%)	10 (45.5%)	4 (18.2%)	6 (27.3%)

because it permits a more effective retaining in place of the permanent filling material by virtue of the overlying scapula and thick interscapular muscles. The anterior approach was used to advantage in an occasional case in our secondary series where planigrams revealed the residual cavity to be located in an anterior position.

For the posterior approach, a vertical incision about 12 centimeters in length is made through the skin, the trapezius and rhomboid muscles half way between the angles of the ribs and the spinous processes of the upper thoracic vertebrae. The scapula is then retracted laterally and the ribs are easily counted by inserting the hand under the scapula and locating the first rib. A portion of the third or fourth rib, approximately eight centimeters in length, is resected subperiosteally and a small incision made through its posterior periosteal bed. Blunt dissection is then employed by means of a small bronchial sponge on the end of a hemostat, until the extrapleural space is located and established sufficiently to admit the tip of the index finger. We then employ finger dissection to free the remainder of the extrapleural space. After the apex is freed, one often is unable to reach the mediastinal surface with blunt finger dissection and here a stick sponge is employed. This latter instrument is used under direct vision with a Cameron light which facilitates this step in the operation.

After the extrapleural space is created, the lucite balls are inserted and the wound closed in layers. We have found that closure of the intercostal, rhomboid and trapezius muscles plus approximation of the subcutaneous tissue and skin are sufficient to keep the pack in place.

In those cases in which the anterior approach was used, an oblique incision was made along the course of the second anterior rib and the pectoralis major muscle divided in the direction of its fibers. The insertion of the pectoralis minor muscle was detached with a raspator as the second rib was removed. Entry into the extrapleural space was then effected as in the posterior approach. After insertion of the lucite pack, the severed portion of the pectoralis minor muscle was used to aid in closing the defect and the pectoralis major muscle, subcutaneous tissue and skin were approximated in layers.

Some workers^{5,6} replace the resected rib and suture it *in situ* following plombage, to facilitate holding the pack in place. We tried this in several of our cases but found that it offered no advantage over the usual method of closure.

Results

Our series consists of 26 patients upon whom 30 stages of extrapleural pneumonolysis were performed. The first patient was operated upon in September 1946, and the twenty-sixth, or last patient in June 1947. Twenty-one of our patients are over eight months postoperative and in the remaining four a period of five months has elapsed since their last operation. Although it is realized that some adverse criticism may well arise from a premature presentation of this series, it is felt that many thoracic surgeons who are starting a similar series of cases may profit from our experience and substitute procedures that have proven more reliable through the production of unequivocal results over a period of years. In other words, a series of cases presenting poor results over a relatively short period of 14 months is probably of more value to the reader than a series of good results studied over a period of years, especially if the former procedure is in vogue and being tried in all parts of the country.

In our series the average duration of disease was four and one-half years, with ranges of from one to 24 years respectively. Seventeen of the 26 patients had bilateral disease which varied in character from moderate tuberculous apical infiltration to actual cavitation in the contralateral lung. The average age of the 26 patients was 40.8 years, the youngest was 20 years old, the oldest 58. Four patients had evidence of endobronchial disease which responded to bronchoscopic cauterization with a 30 per cent solution of silver nitrate.

In four of our 26 patients extrapleural cleavage was attempted but was unsuccessful. In three, where cleavage was attempted under an area of thoracoplastic collapse, marked peripleuritis rendered dissection difficult and resulted in entry into the pleural space. Two of these were approached through an anterior incision and one through the usual posterior route. In the fourth, which was performed as an initial major collapse procedure through a posterior approach, a lack of pleural symphysis was encountered and a rupture through the thin parietal pleura necessitated abandonment of the dissection.

We shall now discuss results in the remaining 22 patients in whom extrapleural pneumonolysis was successful and allowed the insertion of a methyl methacrylate (lucite) pack in the space so created (See Table I).

In 14 cases the packs were primary, no other major collapse procedures having been attempted. In eight the packs were secondary, or packs performed under an area of thoracoplastic

collapse Throughout the remainder of the discussion, these will be referred to as primary and secondary packs, respectively

Our final results (Table I) show that 12 of our patients closed their cavity and that six actually converted their sputum after operation In the 14 cases represented under the primary pack sub-group, it was found that six attained cavity closure and five showed sputum conversion Of the remaining eight cases, representing the secondary packs, six had closed their cavities but only one demonstrated actual conversion of his sputum from positive to negative It should be emphasized, however, that the low percentage of sputum conversions reported in our latter group did not include the four that were negative prior to, and after operation and in whom the pack was inserted merely to obliterate a residual cavity

It was mentioned that 17 of our original 26 patients had contralateral disease However, in the results summated from our 22 successful cases, only one of the nine included in our primary group, and one of the three in the secondary series failed to convert their sputum because of contralateral disease The re-

TABLE II
Fate of Cavities as to Size and Type in Primary Series

Size cm	Type of Cavity	— C A V I T Y —		— S P U T U M —	
		Closed	Unclosed	Positive	Negative
0 - 05	Pinner II				
	Pinner III	1	2	2	1
05 - 10	Pinner II	2		1	1
	Pinner III				
10 - 15	Pinner II	1	1	1	1
	Pinner III				
15 - 20	Pinner II				
	Pinner III		2	2	
20 - 25	Pinner II				
	Pinner III	1	1	1	1
25 - 30	Pinner II	1			1
	Pinner III				
30 - 35	Pinner II		1	1	
	Pinner III				
35 - 40	Pinner II		1	1	
	Pinner III				

maining ten demonstrated open cavities under the area of lucite pack which gave sufficient reason for the positive sputum

The number of lucite balls employed varied from 12 to 59 in the primary group, and from four to 18 in the secondary series. The average number of balls inserted per patient was 27 in the former and 12 in the latter.

Primary packs were placed through posterior incisions by removing sections of the third or fourth rib in 13 cases, and through an anterior incision with removal of a section of the second rib, in one case. In two of these cases supplemental packs were added at another operation, in an effort to close a residual cavity under the initial lucite pack. Both supplemental packs were inserted posteriorly, the initial pack having been introduced anteriorly in one and posteriorly in the other. In neither of these patients receiving supplemental pack under our primary series was cavity closure achieved.

In eight of our secondary pack series the initial pack was inserted through a posterior approach. The regenerated ribs overlying the cavitory area were removed thus affording access to

TABLE III
Fate of Cavities as to Size and Type in Secondary Series

Size cm	Type of Cavity	— C A V I T Y —		— S P U T U M —	
		Closed	Unclosed	Positive	Negative
0-05	Pinner II				
	Pinner III				
05-10	Pinner II				
	Pinner III				
10-15	Pinner II	1	1		2
	Pinner III		1	1	
15-20	Pinner II	2		1	1
	Pinner III				
20-25	Pinner II	1			1
	Pinner III				
25-30	Pinner II				
	Pinner III				
30-35	Pinner II	1		1	
	Pinner III				
35-40	Pinner II	1			1
	Pinner III				

the extrapleural space In two of these, in which postoperative planigrams revealed residual cavitation following the initial pack, a supplemental pack was inserted through an anterior approach with removal of a portion of the second rib Cavity closure was obtained in both, and sputum conversion was accomplished in one Contralateral disease explained the failure of conversion in the other case

We have employed Pinner's⁷ classification in grouping the types of cavities

Type I Cavities without established walls

Type II Cavities with young fibrous walls

Type III Cavities with old fibrotic walls

Of our combined successful lucite pack cases,—that is, both primary and secondary, 14 had Pinner Type II cavity and eight Pinner Type III (see Tables II and III) No case with Pinner Type I cavity would be suitable for this type of collapse procedure and hence, it will be omitted from this discussion The diameters of these cavities varied from 0.5 cm to 4 cm, the average size being two centimeters in the 22 cases In each patient included under the primary pack group, the cavity was located above the level of the first anterior interspace and in the majority of cases it was at the level of, or above the first anterior rib

Of the seven Type II cavities in the primary group, three converted their sputum and four attained cavity closure In the secondary group of seven Type II cavities, one patient converted his sputum (four of these patients were negative prior to and after operation), and six obtained cavity closure

Of the seven patients having Type III cavities in the primary group, two closed their cavities and converted their sputum The other five remained persistently positive on direct smear and their cavities failed to close Only one of our secondary group had a Type III cavity This remained open and his sputum failed to convert In the secondary series the prethoracoplasty roentgenogram determined the type of cavity rather than the planigraphic study of the collapse area after thoracoplasty We felt justified in selecting the prethoracoplasty film in that our cases are kept on the surgical ward until cavity closure and conversion are achieved Hence, if a residual cavity was located on planigraphic study following thoracoplasty, only an interval of from four to six weeks would have elapsed between his last stage of thoracoplasty and insertion of the lucite pack We felt relatively certain that the nature of the cavity would change but little, so far as its classification into Pinner's types is concerned, during this period of time, despite the distortion of its original configuration by the imposed thoracoplastic collapse

Complications of Extrapleural Pneumonolysis with Plombage

We know of no operation in thoracic surgery that offers so wide a variety of complications, both early and late, as does extrapleural pneumonolysis with plombage. Throughout the literature long lists of complications were mentioned and these were altered but little by the introduction of the new plombé materials during the evolution of the procedure. In the following paragraphs we shall discuss only those complications which occurred in the 26 cases in which extrapleural pneumonolysis was attempted or performed.

In our series of extrapleural pneumonolyses with lucite plombage the operative complications were minimal but the postoperative complications were many. In four cases perforation of the pleura occurred. Three of these were in our secondary series, performed under an area of thoracoplastic collapse, and the marked peripleuritis encountered was responsible for the ultimate rupture into the pleural space. In the other case, a member of the primary group which includes those cases in which this operation constituted the initial major collapse procedure, a thin parietal pleura plus the lack of pleural symphysis over the diseased area permitted rupture into the pleural space.

In two of our cases, both of which were included in the secondary series, a mild hemorrhage occurred during dissection. In each of these the bleeding was controlled after inserting a warm saline pack over the area for a few minutes. In no instance was hemorrhage a major problem in the 30 operations of pleurolysis.

Only one of our patients developed an effusion around the lucite pack. This was diagnosed on the fourth postoperative day at which time 200 cc. of serous fluid was aspirated from the extrapleural space. No further accumulation of fluid occurred following this single aspiration.

One patient developed dyspnea. In this instance 59 balls were placed in the extrapleural space with the production of so effective a collapse that the patient's respiratory reserve was increased. In this patient the lucite pack was removed on the postoperative day and an extrapleural pneumothorax was instituted. In only one other case was so massive an extrapleural pack employed. No respiratory embarrassment followed institution of the 50 balls in this patient, but six weeks after an erosion of the pack into the cavity necessitated it. A broncho-cavitary-extrapleural fistula persists having a cutaneous component upon removal of the pack.

In another patient in which 31 lucite balls were used to compress an apical cavity, rupture through into the cavity occurred.

seven months after the initial operation which resulted in abscess formation in the lower portion of the extrapleural space. Again, a bronchocutaneous communication occurred following removal of the pack.

We did not encounter a single superficial wound infection, however, one patient in the secondary series developed a pyogenic empyema five days after insertion of the pack. The latter was removed and the extrapleural space obliterated itself over a period of two months by third-intention healing.

Mild hemoptysis occurred in three patients on the operative or first postoperative day. Stocklin⁸ mentioned the occurrence of mild hemoptysis in such cases and attributed it to cavity wall approximation with a rubbing together of the opposing walls.

In one case in the secondary series, a lucite ball migrated to the cervical area causing pressure symptoms referable to brachial plexus and subclavian artery compression. Figure 12 shows this ball in the cervical area. Later it was removed through a cervical incision with subsequent alleviation of symptoms. In another case in which a primary pack with subsequent supplemental pack was inserted through an anterior incision, the cavity failed to close and removal of the pack was performed four months after the supplemental operation. On entering the extrapleural space we found that five lucite balls had eroded into the mediastinum and were found around the pericardium and great vessels.

In another of our primary group of cases in which a supple-

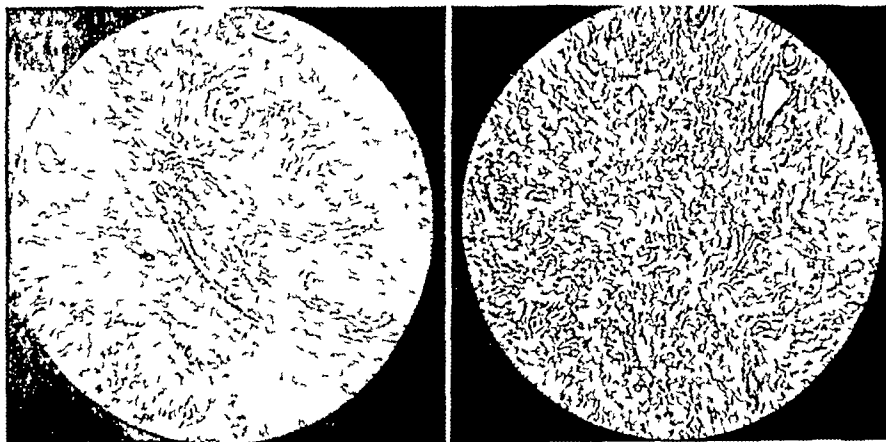


FIGURE 1

FIGURE 2

Fig 1, Case 2 Photomicrograph of dense collagenous tissues surrounding lucite balls showing fibrosis and foreign body reaction. The parts are hyperemic and round cell infiltration is noted. Scattered and grouped granulomata are demonstrable (Hematoxylin and eosin stain). —*Fig 2, Case 1* Photomicrograph of fibrous tissue surrounding lucite balls. Groups of wide blood capillaries and an occasional small accumulation of round cells, plasma cells, and histiocytes are demonstrable throughout this fibrous matrix (Hematoxylin and eosin stain).

mental pack had been employed, an elective removal of the pack with concomitant first-stage posterolateral thoracoplasty was undertaken. Two days later the patient developed a broncho-cavitary-extrapleural communication which necessitated reopening of the extrapleural space to secure adequate drainage of the area. The wound is slowly healing by third intention but the broncho-cutaneous communication persists.

As to methyl methacrylate (lucite), we have found that this substance is far from being the optimum filling material. We have encountered such complications as erosion through the cavity wall both early and late, empyema of the extrapleural space following its introduction, and migration of the lucite balls into both mediastinum and cervical region. In one instance in which the lucite pack was removed and microscopic examination made of the fibrous matrix surrounding the pack, an occasional translucent particle about 20 to 30 micra in diameter and suspicious of lucite was seen in the sections. It is our opinion that through friction minute particles were rubbed off and their presence in the tissues caused a foreign body reaction (Fig 1). No acid-fast bacilli were demonstrable in the sections. In the other cases no granulomata were noted, the microscopic picture revealing fibrous tissue containing lymphocytes, histiocytes and plasma cells (Fig 2). This was the typical picture found in the fibrous tissue matrix surrounding the lucite pack.



FIGURE 3



FIGURE 4

Fig 3, Case 1 Initial roentgenogram demonstrating a 20-cent Type III cavity in right apical region—Fig 4, Case 1 Plaingram showing area of residual cavitation under lucite pack.

In concluding our list of complications, we should like to emphasize the fact that out of our original 22 cases successfully performed, five or 22.7 per cent have had the packs removed and three additional patients are to have removal of the packs within the next month. This will make a total of eight, or 36.3 per cent removal. Of these, three or 13.6 per cent have had the pack removed as an emergency procedure because of complicating factors. Another patient had a lucite ball removed from the cervical area subsequent to its migration into this region.

In the light of these results we hesitate to advise the use of lucite pneumonolysis even for those cases which present ideal indications. When the facts are faced, it is apparent that the extrapleural operation is available for a class of patients who are unsuitable candidates for thoracoplasty, and we cannot expect this type of patients to survive the serious complications and accompanying high morbidity that are inevitable in a large percentage of these cases.

After evaluating the final results as to cavity closure and sputum conversion, and including our complications which are far too numerous, we feel that extrapleural pneumonolysis with plomage leaves much to be desired, irrespective of the type of plombe employed, and are convinced that it has not withstood the test of careful scientific investigation over the past half-century.



FIGURE 5



FIGURE 6

Fig 5, Case 2 Initial roentgenogram demonstrating a 40-centimeter Pinner Type II cavity in the left apical region—*Fig 6, Case 2* Planigram of collapse area under lucite pack after addition of a supplemental pack. Large ballooned cavity is still demonstrable.

Exemplary Cases

Five exemplary cases have been selected from our lucite pneumonolysis series which demonstrate some of the results and complications accompanying this procedure. These case reports are presented below with brief histories and illustrations.

Case 1 A P, age 50. Duration of disease, three years. Right extrapleural pneumonolysis was performed February 7, 1947 through a posterior incision, 25 lucite balls were inserted in an effort to close a small fibrocavernous Pinner Type III lesion, 2.0 centimeters in diameter, located above the level of the first anterior rib (Fig 3). This operation and a supplemental operation with the addition of eight more lucite balls failed to close the cavity (Fig 4). Upon subsequent removal of this pack, five balls were found to have eroded through into the mediastinum and were located around the great vessels and the pericardium.

Case 2 W A, age 22. Duration of disease, three years. Left extrapleural pneumonolysis was performed January 2, 1947 through a posterior approach, 13 lucite balls were inserted in an effort to close a four-centimeter Pinner Type II cavity at the level of the first anterior rib (Fig 5). Following this procedure a residual cavity was demonstrated and a supplemental pack was inserted comprising 12 lucite balls. Postoperative planigrams (Fig 6) revealed the presence of a large tension type of cavity under the area of lucite pack. In later serial roentgenograms this cavity would actually increase and decrease in size from time to time.

This case demonstrates the futility of attempting to close a tension type of cavity with this procedure.

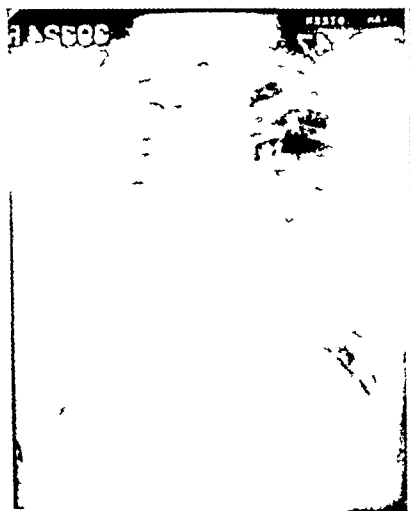


FIGURE 7



FIGURE 8

Fig 7 Case 3. Roentgenogram demonstrating 10-centimeter Pinner Type III cavity in apex of left lung.—*Fig 8* Case 3. Film demonstrates collapse produced by insertion of 15 lucite balls in left extrapleural space. No residual cavitation is demonstrable.



FIGURE 9

FIGURE 10

FIGURE 11

Fig 9, Case 4 Bilateral planigram demonstrating a small 0.5-centimeter Pinner Type III cavity in the apex of left lung —*Fig 10, Case 4* Planigram of area under left lucite pack showing small 0.5-centimeter residual cavity —*Fig 11, Case 5* Bilateral planigram demonstrating residual cavity in area of left thoracoplastic collapse. Fibrocavernous lesion is seen in the contralateral apical area

Case 3 C R, age 36 Duration of disease, one year A left extrapleural pneumonolysis was performed through a posterior approach for closure of a 10-centimeter Pinner Type III cavity in the left apex, above the level of the first anterior rib (Fig 7)

In this instance insertion of 15 lucite balls in the extrapleural space effected closure of the cavity (Fig 8)

Case 4 C C, age 50 Duration of disease, five years Patient had a right two-stage, six-rib, posterolateral thoracoplasty in May, 1946 A postoperative bilateral planigram revealed a small 0.5-centimeter Pinner Type III cavity in the apex of the left lung above the level of the first anterior rib (Fig 9) Through a posterior incision 19 lucite balls were placed in the left extrapleural space Planigrams taken after this procedure revealed a small residual cavity under the area of lucite pack (Fig 10)

Case 5 J J, age 55 Duration of disease, eight years Previous therapy consisted of a left, three-stage, seven-rib, posterolateral thoracoplasty in September, 1946 Following this operation planigrams revealed a large residual cavity under the thoracoplastic collapse (Fig 11) On March 17, 1947 a left, extrapleural pneumonolysis was performed through a posterior incision and nine lucite balls inserted The patient later developed symptoms referable to brachial plexus and subclavian artery compression Roentgenograms revealed the presence of a lucite ball in the cervical region adjacent to the area occupied by these structures (Fig 12) Removal of this ball through a cervical incision secured alleviation of symptoms Figure 13 shows the absence of the cervical lucite ball with closure of the cavity under the lucite pack



FIGURE 12

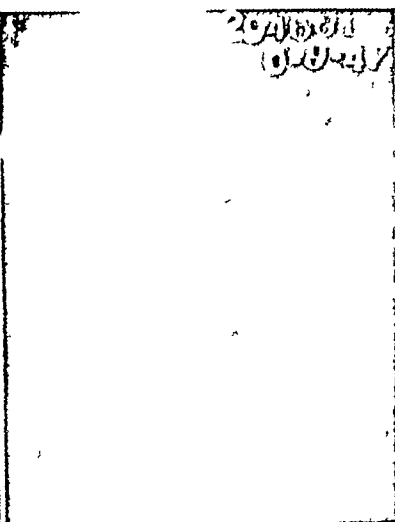


FIGURE 13

Fig 12 Case 5 Roentgenogram following insertion of nine lucite balls in left extrapleural space over residual cavity area One ball migrated into the neck and caused symptoms referable to brachial plexus and subclavian artery compression—*Fig 13*, Case 5 Planigram showing area of lucite pneumonolysis following removal of lucite ball from cervical area No residual cavity is demonstrable in the collapsed area

SUMMARY

- 1) The indications for extrapleural pneumonolysis with lucite plombage are briefly presented and discussed
- 2) The operative technique is described
- 3) Results and complications in 26 patients upon whom 30 stages of extrapleural pneumonolysis were performed are reviewed. The low percentage of cavity closure and sputum conversions plus the numerous complicating factors occurring with this procedure caused us to abandon its use on our thoracic surgical service
- 4) Five cases are reported with illustrations to demonstrate some of the results and complications following the use of this operation

RESUMEN

- 1) Se presentan y discuten sucintamente las indicaciones para la neumonolisis extrapleural y plomaje con *lucite*
- 2) Se describe la técnica operatoria
- 3) Se revisan los resultados y complicaciones en 26 pacientes sometidos a 30 tiempos de neumonolisis extrapleural. El bajo porcentaje de cierre de cavernas y conversión de esputos, además de las numerosas complicaciones que acompañan a este procedimiento, nos obligaron a abandonar su empleo en nuestro servicio quirúrgico de torax
- 4) Se refieren cinco casos ilustrados para demostrar algunos de los resultados y complicaciones subsiguientes al empleo de esta operación

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Systemic Blastomycosis*

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Introduction

Blastomycosis is a disease caused by the organism *Blastomyces dermatitidis*. It is not rare yet is by no means common, and case reports are not numerous. For this reason, further case presentation is justifiable for whatever additional light it may shed upon the disease. Martin and Smith,¹ who reviewed the literature up to 1939, considered only 80 (23 per cent) of the 347 reported cases as proved. They added 13 new cases of their own. In 1942, Baker² analyzed the tissue in 23 cases of human blastomycosis occurring in a 10 year period. Ten of these cases were of the generalized type, some had been previously reported.

Jacobsen and Dockerty³ reported on four cases of blastomycosis of the epididymis and stated that they represent only a fraction of the total number of patients with proved blastomycosis, from 1910 through 1942, 62 patients in all were seen. 56 were males and 6 females. Of the males, 12 had systemic blastomycosis and 44 had the cutaneous type. No attempt is made here to bring the total number of reported cases up to date, and the literature has already been ably reviewed.^{1,4}

At Muirdale Sanatorium the following study was made from December 1934 to August 1948. During that time 11 cases of human systemic blastomycosis came under our observation. All entered as presumable cases of pulmonary tuberculosis. Two had both diseases.

Mycology

Gilchrist, in 1894, discovered the yeast-like organism in section of diseased skin and named it *Blastomyces dermatitidis*. It is round or oval, varies from 10 to 15 microns in diameter, has a highly refractive, double-contoured border and may be seen singly or in clusters. Budding forms are practically always present. The organisms will grow in two to four days. Although in some

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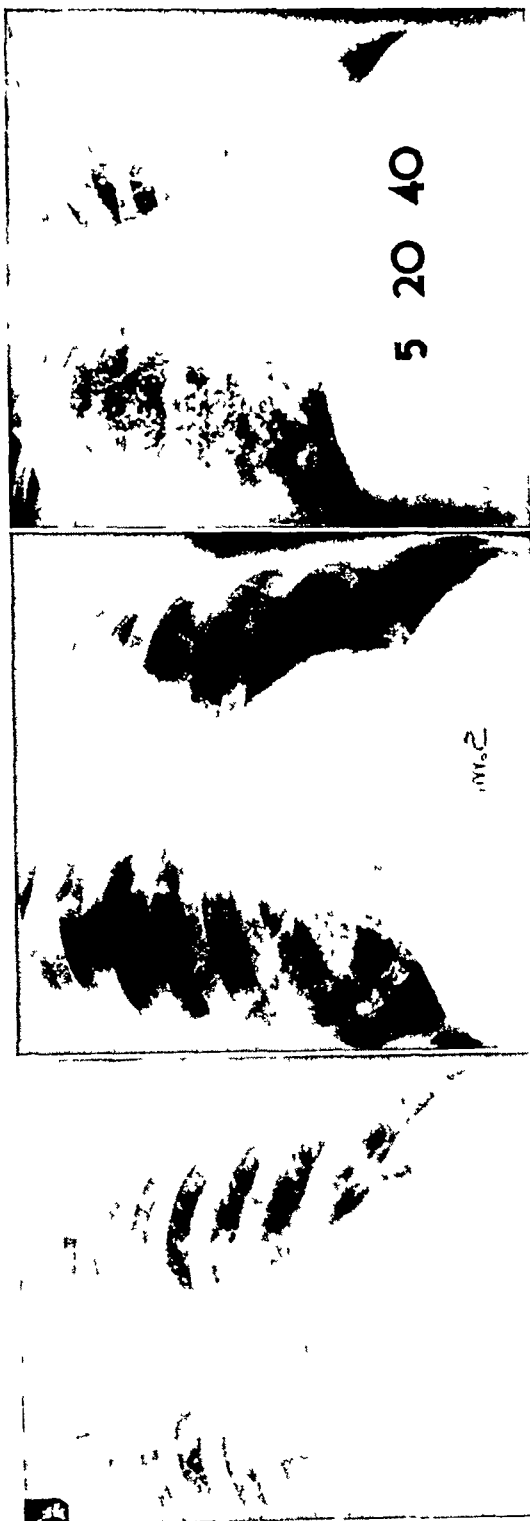


FIGURE 1

Fig 1, Case 1 T D, white, male, 41 years old, road construction worker. Respiratory symptoms six months prior to admission. Later he developed subcutaneous abscesses on his right hand, wrists, and left ankle. Died January 1936, just 18 months after the onset of symptoms. Postmortem examination revealed generalized blastomycosis involving the lungs, liver, kidneys and spleen—*Fig 2, Case 2* S M, white, male, age 43, crane operator. Respiratory symptoms of two months duration and deep non-painful subcutaneous abscess in the left gluteal area and the left arm. Bronchoscopic examination revealed nearly a complete occlusion of the left main bronchus. Pus from one of the abscesses revealed *B. dermatitidis*, but guinea pig inoculation was negative for blastomycosis and tuberculosis. Treatment consisted of saturated solution of potassium iodide by mouth, 40 mm t i d. The patient died from terminal meningitis on March 10, 1937, four months following the onset of symptoms. Postmortem examination revealed a generalized blastomycosis with meningeal involvement—*Fig 3, Case 3* F P, white, male, age 47. One month prior to admission he became sick with fever, chills, cough, expectoration and hemoptysis. Sputum examination revealed tubercle bacilli and *B. Dermatitidis*, both of which were verified on culture. Death occurred one month later. Treatment was palliative. No iodides were given.

FIGURE 2

FIGURE 3

cases it may take two weeks, on Sabouraud's agar medium or dextrose blood agar. Differentiation from other fungi, particularly *Coccidioides immitis* and *Torula histolytica*, may require a trained bacteriologist or mycologist.

Mode of Infection

The sources of the infection and the method of its transmission remain an unsolved problem.⁵ As far as known, direct transmission from man to man is rare. The portal of entry is thought to be by direct inoculation in the primary cutaneous disease and by respiratory tract in the systemic type.

The organism is widespread in nature, and individuals of practically all ages have been infected, the ratio between male and female is reported as 9 to 1 (nine of our 11 cases were males). There does not appear to be any occupational relationship to the disease, but it is reported as more common among poor people.

Pathology

The microscopic picture is somewhat like tuberculosis, and blastomycosis is occasionally mistaken for tuberculosis, as in our case 2. Medlar⁶ says the only way to tell the difference between the two diseases is to find the organism. Baker² believes a differentiation can be made on the histological basis and indicates that human blastomycosis is primarily pyogenic with predominance of polymorphonuclear neutrophils.

The blood picture does not present unusual findings. Most of our cases revealed a leucocytosis with an increase in neutrophils and all had a rapid sedimentation rate of the erythrocytes.

Clinical Manifestations

The disease manifests itself in two forms: the cutaneous which is either primary or secondary and the systemic in which any organ of the body can be involved. In the primary cutaneous type, papular and pustular lesions usually appear on the face, neck or the extremities. Unless there is extensive involvement the patient is not sick. Necropsy records⁵ disclose that 95 per cent of the systemic cases present some degree of pulmonary involvement. All of our cases were of the systemic variety and eight developed secondary skin lesions in the form of subcutaneous abscesses. All had respiratory symptoms, characterized by cough, expectoration, hemoptysis and chest pain; they had loss of appetite and weight, fever and chills. Some patients have a paucity of symptoms. Occasionally a case may show moderately severe toxicity with small involvement.



FIGURE 4



FIGURE 5



FIGURE 6

Fig 4, Case 4 E V, white, male, age 29 His respiratory symptoms were of six weeks' duration Bronchoscopic examination revealed a moderate narrowing of the right upper lobe bronchus Blastomycetes were found in the sputum on wet smear, and cultures were positive for this organism—*Fig 5, Case 5* R R, white, female, age 36, bookkeeper Ten weeks before admission she developed "stomach flu" and one week later pain in the lower right chest The day before admission to Maudsley 500 cc of clear fluid were aspirated from the right pleural cavity This fluid, inoculated into a guinea pig was negative for tuberculosis Her symptoms were loss of appetite, loss of weight, right chest pain, fever and chills Bronchoscopic examination revealed a bulging of the medial bronchial wall at the level of the right middle and lower lobe orifice A second chest aspiration revealed pus, and blastomycetes were present on wet smear This was confirmed by culture The treatment consisted of saturated solution of potassium iodide, reaching a dose of 90 mm, t.i.d The patient died nine months from onset of symptoms Postmortem examination revealed generalized blastomycosis and two cavities were found in the right lung, measuring 7 cm and 4 cm in diameter—*Fig 6, Case 6* J D Mc, colored, male, age 51, molder (10 years) In January 1941 he developed respiratory symptoms His sputum was positive for tubercle bacilli Two weeks after admission he complained of a toothache and pain over the left jaw Examination revealed a deep-seated non-painful nodule, about the size of a navy bean, over the left masseter area Over a considerable period of time the abscess gradually increased in size and became fluctuant Four more deep-seated slightly painful abscesses developed two each over the right and left scapulae Pus aspirated from these abscesses on June 11 revealed blastomycetes that were positive on all cultures Treatment consisted of saturated solution of potassium iodide the maximum dose being 24 mm, t.i.d The abscesses were frequently aspirated, were finally broken down and discharged small amounts of pus through the needle puncture-wound The abscesses were irrigated with tincture of iodine and complete healing occurred in about four weeks

Diagnosis

Skin tests and complement fixation reaction are advantageous and should be used in obscure cases¹ The diagnosis, however, is established by the demonstration of the *B dermatitidis* which may be recovered from various body secretions or may be demonstrable in biopsy Culture methods of diagnosis,² even without sections showing characteristic tissue response, have proved to be reasonably accurate since *B dermatitidis* has not been shown to be a common secondary invader of human lesions or exudates Mice are recommended for animal inoculation since they are the most susceptible laboratory animals

Roentgenogram

There is nothing characteristic in the roentgenologic appearance, and we agree with Reeves⁷ that lung lesions are variable from dense pneumonic masses to milary distribution Five of our cases had upper lobe consolidations, and one of them developed a typical bronchogenic spread to the opposite side It has been stated⁸ that most cases show dense masses extending out from the hilum Cavities¹ are reported to be uncommon and not over 1 cm in diameter Capdehourate and his associates⁹ report one case with a large pulmonary cavity

Treatment

A number of drugs have been used, including the arsenicals, colloidal copper and gold, thymol, sulfonamides, ether,^{4 10} penicillin, and many others

The sulfonamides have not proved very beneficial, although Albert¹¹ reports a case of extensive cutaneous blastomycosis that did not respond to potassium iodide, but was cured by sulfathiazole and sulfapyridine Noojin and Callaway,¹² in vitro experiment, tried seven of the sulfonamides, and none was effective at levels as high as 10 mg per 100 cc Sulfadiazine, the most efficient drug used, was not decidedly fungistatic until a concentration of 125 mg per 100 cc was reached They suggest the use of sulfanilamide for topical therapy of cutaneous blastomycosis Frank and Taylor¹³ reported on a case of cutaneous blastomycosis complicated by meningitis where they used iodides, sulfonamides and penicillin, but the patient died Penicillin is contraindicated in blastomycosis^{14 15} Meyer and Ordol¹⁷ used *B dermatitidis* in vitro experiment and showed that streptothricin and gliotoxin were fungistatic while streptomycin and penicillin were not The organism was highly resistant to streptomycin

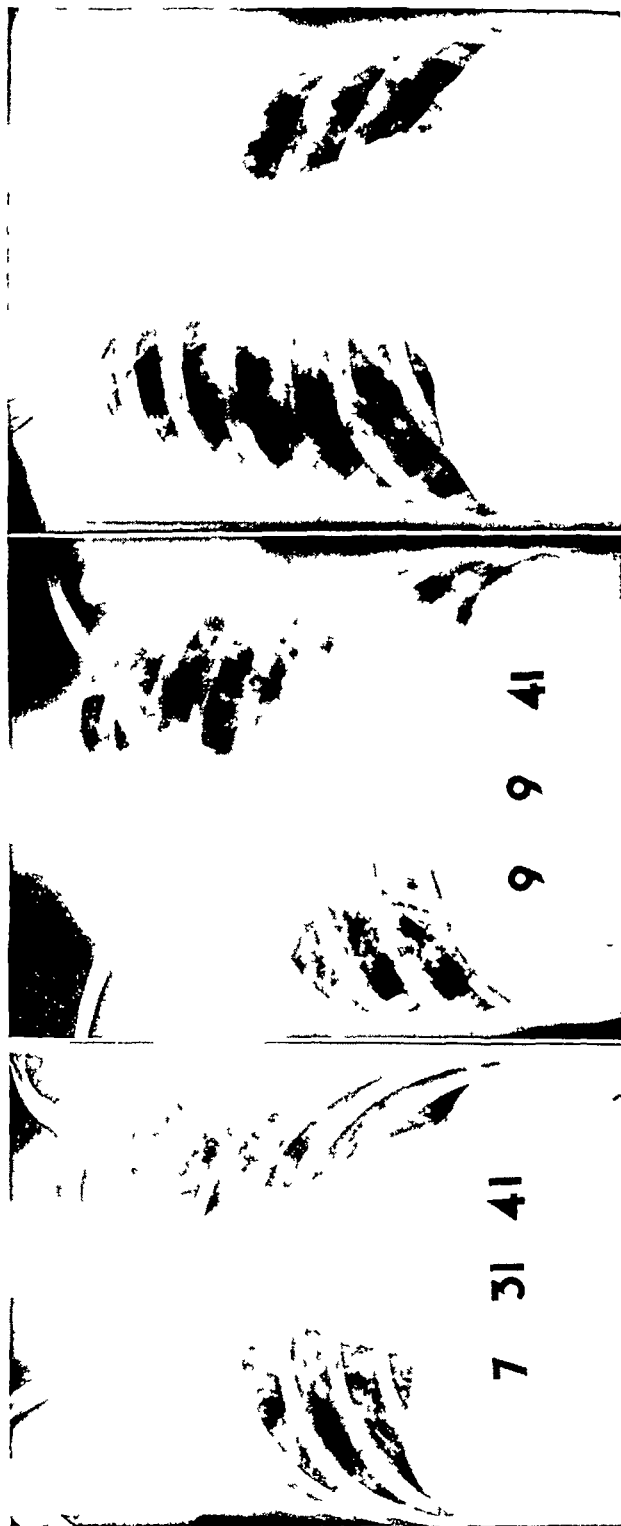


FIGURE 7A

Fig 7A Case 7 H D, white male, age 26, garage mechanic. He entered Murdale with marked respiratory symptoms, and with a past history of repeated chest colds for 18 months. His general condition was poor. Blastomycetes were recovered from the sputum and from one small abscess on his left forearm. No iodides were given. A postmortem examination (performed 20 months from onset of symptoms and seven weeks after admission to Murdale) revealed generalized blastomycosis with a 5 cm cavity in the right apex.—*Fig 7B, Case 7* Bronchogenic spread to the left base.—*Fig 8, Case 8* D G, white, male, age 39, office manager. The patient was well until six weeks prior to admission when he developed cough, expectoration blood streaked sputum and fatigue. Sputum examination at Murdale were negative for tubercle bacilli but revealed *B. dermatitidis*. The treatment consisted of sulfadiazine which was started February 7 and continued for 17 days. The blood levels reached a maximum of 10 mg per 100 cc of blood. There was no apparent result with this drug and saturated solution of potassium iodide was started. The maximum dose was 50 mm t i d and the response was gratifying.

FIGURE 7B

FIGURE 8

The most commonly used drugs are the iodides, alone or in combination with various other agents. According to Martin and Smith¹⁶ iodides may aggravate the condition, particularly when the patient is highly allergic to the fungus. Therefore, by means of skin testing they ascertain the degree of sensitivity and reduce it by vaccine therapy, if necessary, before starting the iodides. They feel that this procedure is extremely important.

Prognosis

The prognosis is good in the primary cutaneous types, but a 90 per cent mortality is reported in the systemic type.

Discussion

In systemic blastomycosis it is not difficult to understand the erroneous diagnosis of pulmonary tuberculosis which is so frequently made. Even the histologic pictures of the two diseases are similar. An accurate diagnosis is established when the organism is recovered. Cultural methods are reliable, and in our experience animal inoculation was not helpful. Mice were inoculated with cultural material from cases 3 and 4, and pleural fluid from case 5 was inoculated into a guinea pig, but blastomycosis did not develop in any of the animals. In our 11 cases, there do not appear to be any occupational, racial, or economic factors contributing to the disease. Two of our cases were Negroes. Twenty-eight per cent of other reported cases were Negroes,¹ but this high percentage may have been due to the population makeup of particular areas.

Pulmonary involvement is practically always present, but it could not be proved conclusively by roentgenograms in cases 3 and 4 where the presence of silicosis and tuberculosis complicated the picture. The supposed characteristic of hilar involvement was present in cases 1 and 9. In case 5 the lung field was obscured by pleurisy with effusion, but the bronchoscopic examination indicated a mediastinal mass. Large pulmonary cavities are not common, but cases 5 and 7 had cavities measuring 5 cm. and 7 cm., respectively, discovered on postmortem examination.

In spite of the report¹¹ that sulfathiazole and sulfapyridine were more effective than iodides, iodides in large doses were apparently effective in four of our cases. These patients have been observed from three to eight years following the onset of disease, and there has been no evidence of recurrence. We have given large doses of potassium iodide to points of intolerance and recommend that the drug be continued for a long period of time well beyond the stage of apparent cure.

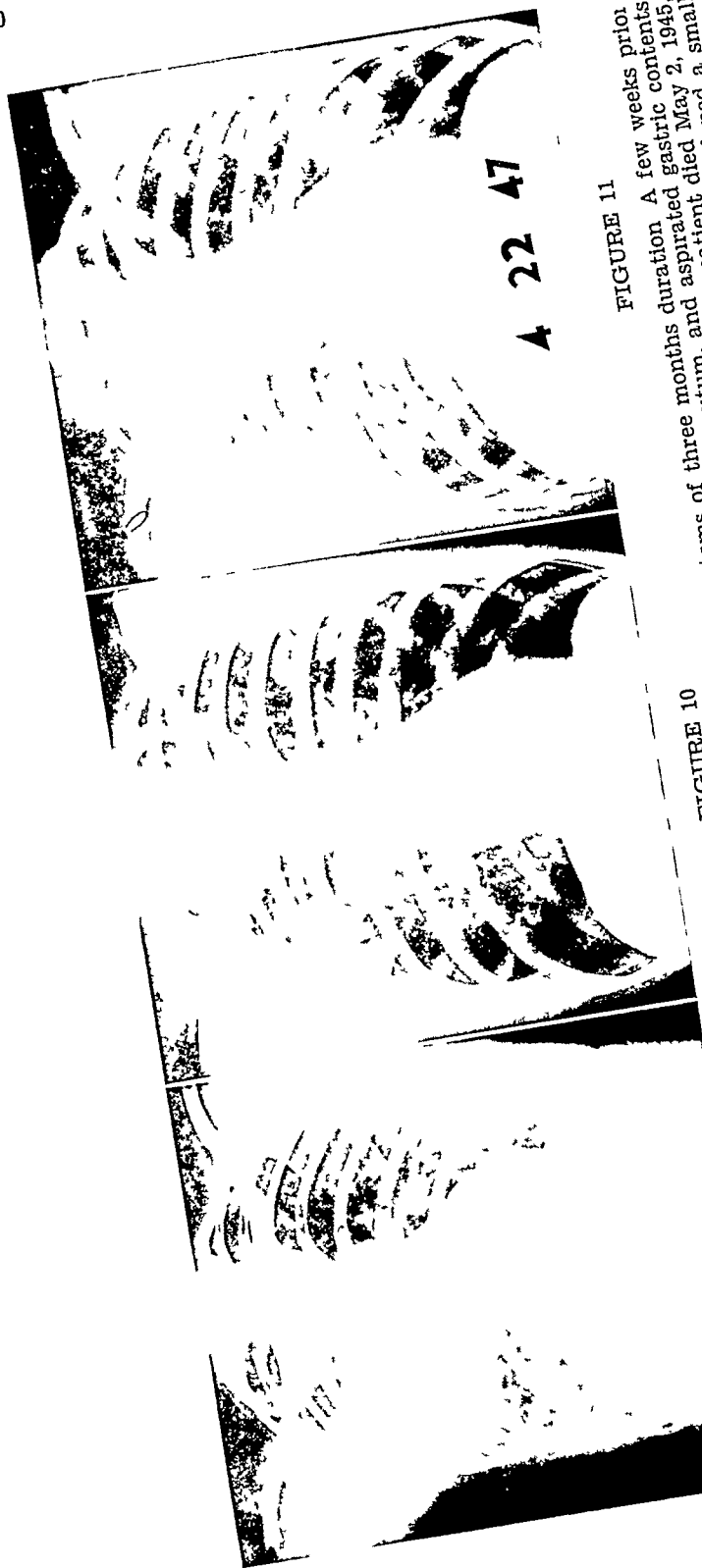


FIGURE 10

FIGURE 11

FIGURE 9

Fig 9, Case 9 M J, colored female, age 38, housewife. She had respiratory symptoms of three months duration. A few weeks prior to admission a small abscess developed over the right mastoid area. Pus from the abscess, sputum, and aspirated gastric contents showed typical B dermatitis by microscopic and cultural methods. No tubercle bacilli were present. The patient died May 2, 1945, eight months after onset of symptoms. —Fig 10, Case 10 S M, white, male, age 39, machinist. In April 1945 he developed a small abscess on the right ankle which was incised and drained. Subsequently he developed an abscess on the left knee and right ankle, and the right side of the face condition. The chest roentgenogram revealed a few scattered calcified areas in the left ear, right hand, and the second interspace anteriorly. t i d, was started to the right ankle, left knee, and face. At present his apex and a soft lesion in the second interspace anteriorly. t i d, was started to the right ankle, left knee, and face. At present his general condition is excellent, he has been working as a machinist in nature, with a loss of 22 pounds in weight. Sputum examination revealed no tubercle bacilli but did show B dermatitis. He was started on saturated solution of B dermatitis. About three weeks postoperatively his disease disseminated with spread of symptoms various parts of his body. He died eleven months after the onset of symptoms.

SUMMARY

1) Eleven cases of systemic blastomycosis are reported. Seven are dead, four are living. Eight, seven, four and one-half, and three years, respectively, after the diagnosis was established.

2) Pulmonary symptoms were predominant, and except when tuberculosis coexisted with the blastomycosis, pulmonary tuberculosis was the initial diagnosis.

3) The roentgenologic appearance may simulate practically any type of pulmonary pathology. It has no particular pattern. Five of our cases showed upper lobe consolidation.

4) In two of our cases large pulmonary cavities were present, this is contrary to the usual reports.

5) Cutaneous manifestations usually are present, and should be searched for because small innocent-looking abscesses may yield the organism.

6) Sputum examination usually will reveal the blastomyces either on wet smear or culture. Animal inoculation may be necessary. In our experience it was disappointing.

7) Biopsy material should be examined carefully and the diagnosis made only when the organism is found.

8) Iodide was the drug of choice in this series.

9) One case in which pulmonary resection was performed ended fatally.

RESUMEN

1) Se refieren once casos de blastomicosis orgánica. Siete han muerto, cuatro han vivido ocho, siete, cuatro y medio y tres años, respectivamente, desde que se les hizo el diagnóstico.

2) Predominaban los síntomas pulmonares y, exceptuando los casos en los que la tuberculosis coexistía con la blastomicosis, el diagnóstico inicial fue el de tuberculosis pulmonar.

3) El aspecto roentgenográfico puede imitar casi cualquier tipo de patología pulmonar. No tiene ningún patrón especial. En cinco de nuestros casos se notó consolidación en lóbulos superiores.

4) En dos de nuestros casos había grandes cavernas pulmonares, lo que difiere de los informes usuales.

5) Por lo general, ocurren manifestaciones cutáneas y debe buscárselas porque es posible encontrar el microbio en abscesos pequeños y aparentemente inocuos.

6) Exámenes del esputo generalmente demuestran el blastomiceto ya en frotis húmedos o en cultivos. A veces es necesario inocular a animales aunque en nuestra experiencia ello no ha dado buenos resultados.

7) Debe examinarse cuidadosamente el tejido obtenido en biop-

sias, y sólo debe hacerse el diagnóstico cuando se encuentre el microbio

8) Los yoduros fueron las drogas de elección en esta serie

9) Terminó fatalmente un caso en el que se hizo una resección pulmonar

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Arthralgia as a First Symptom of Pulmonary Lesions*

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It is the purpose of this communication to emphasize that arthralgia may be the earliest manifestation of hypertrophic pulmonary osteoarthropathy and consequently, at times, the earliest symptom of intrathoracic disease. That clubbing of the fingers is an early manifestation of hypertrophic pulmonary osteoarthropathy was suggested by Marie¹ in 1890, Bamberger² in 1891, and shortly after by Lefebvre,³ Thompson,⁴ Landis,⁵ and others. Locke,⁶ in 1915, determined conclusively that clubbed fingers are an early phase of hypertrophic pulmonary osteoarthropathy. "Simple clubbing of the fingers and secondary hypertrophic osteoarthropathy should be considered as identical, the former representing an early stage of the latter." He reiterated that in the majority of instances hypertrophic osteoarthropathy is secondary to a primary pathological process involving the organs of the thorax.

Van Hazel,⁷ in 1940, stressed the fact that joint manifestations, when occurring rapidly, in the absence of pulmonary symptoms, may be interpreted as arthritis. This error precludes an early diagnosis of the pulmonary pathology which may be a malignant neoplasm. Pain, although not always present in pulmonary osteoarthropathy, may be the first symptom of the process. This is of extreme diagnostic importance. Regarding this important point, the literature is deficient. Craig,⁸ Nef,⁹ Van Hazel⁷ and Pavlovsky¹⁰ are among the few who have made the correlation.

Many cases are incorrectly treated for arthritis without the underlying pulmonary disease, frequently a tumor being suspected. Three of Craig's⁸ cases were treated for rheumatism. Six of the seven cases collected by Van Hazel⁷ were treated for arthritis. Locke's⁶ first case had arthritis nineteen months before the first recorded pulmonary symptom, an hemoptysis occurred. This case is an excellent example of arthralgia as the first symptom of hypertrophic pulmonary osteoarthropathy due to a carcinoma of the lung. Of course, in 1915, this was of academic interest only. Nevertheless, he failed to note the diagnostic value of the symp-

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toms It was to be 18 years before the lesion was successfully dealt with¹¹

The diagnostic importance of arthralgia as an early symptom of hypertrophic pulmonary osteoarthropathy is not mentioned in most textbooks of general medicine, monographs concerning symptom diagnosis, and treatises on chest diseases Keller and Callender,¹² Nef, Van Hazel, Brum,¹⁴ Pavlovsky and Poppe¹³ commented on the marked, often immediate relief of arthritic phenomena following resection of the offending lesion This was striking in one of our cases

An attempt was made to collect cases from the literature in which arthralgia was the first manifestation Certainly these do not represent all of them, but the difficulty of such a task is readily appreciated when it is realized that many of the authors whose cases are presented did not note the temporal relation of the arthralgia to subsequent pulmonary symptoms The specific joints involved are not mentioned for they were multiple and varied Many of the patients listed were completely bedridden for months because of "arthritis"

Case 1, Locke, 1915 A 32 year old white male who had arthralgia 19 months before the first pulmonary symptom, an hemoptysis, occurred The case was proved to be a bronchiogenic carcinoma by necropsy three years and 10 months after he first sought medical attention There was marked clubbing of the fingers, and x-ray films showed evidence of periostitis of the long bones

Case 2, Keller and Callender, 1930 A 38 year old Philippino female who had arthralgia 12 months Symptoms and anatomical changes in the joints subsided after resection of a perineural fibroma weighing 660 grams from the pericardium of the right chest She had marked clubbing of the fingers and toes

Cases 3, 4 and 5, Craig, 1937 (3) A 58 year old white female who had arthralgia for seven months before the diagnosis of a neoplasm of the lung was made by x-ray Clubbing was noted after five months of arthralgia

(4) A 58 year old white male who had arthralgia and swelling of the joints three months before clubbing was noted and for 11 months before a diagnosis of carcinoma of the right lung was made by bronchoscopic biopsy He was treated for arthritis for 11 months, and denied pulmonary symptoms during the first three months of his arthralgia

(5) A 45 year old white male who had arthralgia and swelling of the joints for eight months before the diagnosis of carcinoma of the lung was made by bronchoscopic biopsy Clubbing was noted one month after the onset of pain and cough occurred seven months later

Craig suggests "that investigation of the lung should not be overlooked in patients with rheumatism or with changes in the joints appearing without known causes as well as in those with acromegaly"

Case 6, Nef An 11 year old white female who noted arthralgia and clubbing 12 months before a diagnosis of mediastinal tumor was made. Two months later a granulomatous xanthofibroma containing many lymphocytes and plasma cells was surgically removed. The patient experienced immediate dramatic relief from joint pains and fever. She had no symptoms referable to the chest at any time.

Case 7, Brum An 11 year old white female who had malaise, fatigability, and failure to gain weight for four months followed by arthralgia and fever. Five months from the onset of symptoms, a diagnosis of a lung tumor was made by x-ray inspection of the chest. At no time did the patient have cough, sputum, or hemoptysis. The fingers were clubbed. A circumscribed tumor was resected from the right upper lobe and proved to be a myoma of the lung with lymphocytic infiltration. The patient's symptoms responded dramatically to its removal.

Cases 8, 9, 10, 11 and 12, Van Hazel (8) A 46 year old white female who had arthralgia for one month which recurred one year later along with noticeable clubbing and cough. A diagnosis at exploratory operation of carcinoma of the lung was made two years after the onset of initial arthralgia.

(9) A 52 year old white female with arthralgia and swelling of the joints eight months before symptoms of "pressure in the chest" and dyspnea occurred. A diagnosis of pulmonary carcinoma was proved by biopsy. There were marked clubbing of the fingers and hypertrophic pulmonary osteoarthropathy type of periostitis of the long bones of the upper and lower extremities on x-ray inspection.

(10) A 40 year old white female who complained of arthralgia, swelling and stiffness of the joints two months before the first pulmonary symptom of hemoptysis occurred. Five months after the onset a right pneumonectomy was performed for carcinoma. There was dramatic, immediate relief of the arthralgia. Physical examination and x-ray films in this case demonstrated marked clubbing of the fingers and hypertrophic periostitis of the long bones.

(11) A 32 year old female who noted stiffness, arthralgia and swelling of the joints seven months before an anterior mediastinal fibroma weighing 610 grams was removed. This was followed by dramatic relief of arthralgia. There was marked clubbing of the fingers on physical examination.

(12) A 74 year old female who had arthralgia, swelling and clubbing of the fingers eight months before a metastatic fibrosarcoma of the lung was diagnosed by x-ray examination. Pulmonary symptoms and cough appeared 10 months after the onset of arthralgia.

Case 13, Duncan ¹⁵ A 50 year old white male with arthralgia one year before death due to adenocarcinoma of the lung proved by biopsy. No mention was made of pulmonary symptoms. Physical examination revealed marked clubbing.

Case 14, Pavlovsky ¹⁰ An adult male presenting symptoms of arthralgia. No pulmonary symptoms noted. Because of the patient's clubbing a chest x-ray film was taken and an adenocarcinoma of the lung found, which was resected. There was dramatic immediate postoperative relief of pain.

Case 15, Lopez ¹⁶ A 43 year old white male who six months before entry to the hospital suffered arthralgic pains in the hands and feet followed shortly thereafter by fever Two months later he developed pulmonary symptoms of cough and hemoptysis At the time of entry to the hospital he exhibited clubbing of the fingers and toes and necropsy revealed carcinoma of the right lung

Case 16, Berg A 51 year old white male whose first complaint was pain in the legs A diagnosis of rheumatic fever was made and three months later a chest x-ray film revealed a circumscribed opacity in the right upper lobe A right pneumonectomy was performed for an adenocarcinoma of the lung There was immediate relief of arthralgia postoperatively He exhibited minimal or no clubbing of the fingers but x-ray films of the hands and tibia showed some evidence of periostitis

Case 17, Berg A 12 year old white female, congenital luetic, who entered a hospital complaining of arthralgia and swelling of the feet Clubbing of the fingers and toes was noted The patient was treated for arthritis On July 9, 1946, because of progression of her arthritic process, a chest x-ray film was taken in the course of a routine work-up Evidence of a lesion in the left upper lobe was seen There was no pulmonary complaint at any time On September 22, 1946, after a failure of x-ray therapy and sulfarsphenamine therapy, the patient was referred here and the left lung was removed for what appeared to be a malignant tumor Section revealed it to be a cystic granulomatous mass of questionable pathology

Case 18, Berg A 53 year old white male who had arthralgia and swollen joints eight months before entry to the hospital He denied all pulmonary complaints He had received no therapy for his arthritis and while receiving hydrotherapy, the doctor noted clubbing of his fingers and toes and had an x-ray film taken of the chest This revealed a circumscribed shadow, 5 cm in diameter, in the right lung which was resected with immediate dramatic improvement of the arthralgia postoperatively There was an associated effusion in the right knee joint The lesion proved to be a bronchiogenic carcinoma

Case 19, Berg A 62 year old white male coal miner who complained of headache, pain in the neck, shoulder, left arm and leg migrating to the right arm and leg, associated with an effusion of the right knee, two weeks prior to entry There were no pulmonary symptoms whatsoever A diagnosis of fibrositis due to dental caries was then made The referring doctor took an x-ray film of the chest in a routine examination and a hilar shadow was discovered At operation, an undifferentiated carcinoma of the left lung was identified The lesion was not resectable

Case 20, Berg A 49 year old white male who first noted arthralgia in November, 1946 He developed pain and tenderness in both knees and ankles Two months later he observed clubbing of the fingers One year before entry he developed a hacking cough He had an hemoptysis six days before admission At operation, an inoperable carcinoma was found in the left upper lobe

SUMMARY

Arthralgia may be the earliest symptom of intrathoracic disease The patient who presents this complaint should have a thorough

study of his chest including x-ray inspection. The surgical removal of an intrathoracic neoplasm often may bring about dramatic relief of such arthralgia.

RESUMEN

El primer síntoma de enfermedades intratorácicas puede ser la arthralgia. A todo enfermo que se queje de este síntoma debe hacerse un examen completo del tórax, inclusive de radiografías. La excisión quirúrgica de una neoplasia intratorácica a menudo conduce al alivio espectacular de la arthralgia.

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An Unusual Case of Traumatic Diaphragmatic Hernia with Successful Operation

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Numerous classifications have been proposed for diaphragmatic hernia. Most of them are of little practical value from a clinical standpoint. Harrington's¹ classification of diaphragmatic herniae into two main groups, nontraumatic and traumatic, is preferred because of its simplicity. He subdivides the traumatic group into (1) hernia due to indirect injury to the diaphragm and usually the result of a severe crushing injury, and (2) hernia due to direct injury to the diaphragm which is usually the result of a penetrating wound. The following case falls into the latter group and is presented for two reasons. First, the two unusual openings in the diaphragm through which the stomach, colon and the omentum protruded, and second, the prolonged period of observation and clinical study in a hospital before the diagnosis was made.

CASE REPORT

A 42-year old Mexican male was admitted to the Santa Barbara General Hospital on November 21, 1946, complaining of intermittent cramp-like pains in the upper abdomen, nausea with occasional vomiting, cough, fever and chills. The patient had been confined to the county jail since October 4, 1946, at which time following a domestic quarrel, he stabbed himself twice with a knife in the left lower chest. One week later, the patient first began to notice intermittent pains in his epigastrium. The pains were cramp-like in nature, were not relieved by eating food, and at times were accompanied by the regurgitation of undigested food particularly when he forced himself to eat. The patient attributed the symptoms to the change in his usual diet. The complaints gradually increased in severity and the day before admission to the hospital, he developed a non-productive cough and complained of fever and chills. He did not complain of dyspnea at anytime.

The physical examination on admission revealed a well nourished male of normal development and good musculature. The temperature was 101 degrees F, pulse 88, and respirations 18. He coughed frequently during the examination and complained of pain in his left lower chest. Examination of the head, eyes, throat and neck was negative. The percussion note over the left lower chest was flat and the breath sounds were markedly depressed. There were two healed scars from the stab wounds in the left lower thorax in the anterior axillary line. The PMI was slightly displaced to the right. The abdomen was negative throughout as was the remainder of the physical examination. Because of the findings on admission (Fig 1), he was given 35,000 units of penicillin intramuscularly every three hours until December 22, 1946.

An x-ray study of the upper gastro-intestinal tract on admission (Fig 2) showed no organic lesion and it was felt that the stomach was apparently distorted by changes at the base of the left lung

The blood and urine on admission were within normal limits and the blood Kahn and Kline tests were negative On November 23 he vomited undigested food about one hour after his noon meal This was repeated several times within the next few days He had daily bowel movements but complained of hard stools and constipation Because of the persistent vomiting a Wangenstein suction apparatus was inserted on November 29, he was given glucose intravenously, and permitted nothing by mouth except small sips of water It was necessary to follow this regime intermittently until December 9 before he was able to eat without nausea

On December 10 an aspirating needle was inserted into the left pleural space in the posterior axillary line and 30 cc of bloody fluid was withdrawn following which a diagnosis of traumatic hemothorax was made Bacteriologic study of this fluid was negative for pathogenic organisms

Since admission x-ray inspection suggested lung abscess, a bronchoscopy was performed by Dr A R Olsen on December 24 with essentially negative result, except some distortion of the terminal left lower lobe bronchus and the possibility of some compressing lesion was suggested

On January 6, 1947, following the report of acid-fast bacilli on one of three 24-hour sputum specimens, the patient was transferred to the General Hospital Tuberculosis Sanatorium This finding was never confirmed and the acid-fast bacilli were not identified as tubercle bacilli

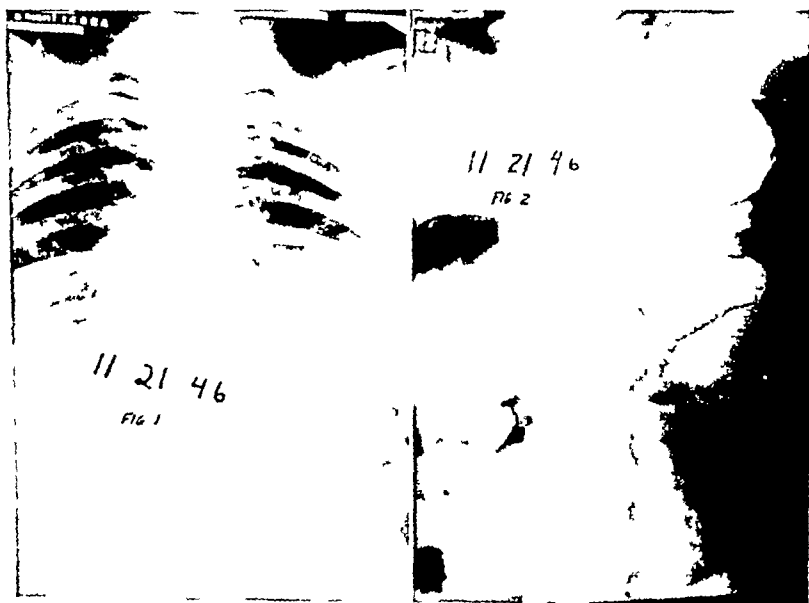


FIGURE 1

FIGURE 2

Fig 1 P A View of chest revealing evidence of fluid and air containing pocket at the base of the left lung suggestive of abscess—*Fig 2* Barium study of stomach the day of admission showing no evidence of organic lesion in the upper gastro-intestinal tract

On admission to the sanatorium 14 consecutive 24-hour sputum specimens were sent to the laboratory for concentration and culture for tubercle bacilli. All were negative. A series of gastric cultures were negative for tubercle bacilli in April, 1947. The Mantoux skin reaction was strongly positive.

Roentgenograms were taken on April 14 and July 8. The clinical diagnosis at this time was subsiding traumatic hemothorax with intense pleural reaction and elevation of the left diaphragm. During this period, the patient had been on a regime of bed rest and had improved clinically. He had gained in weight from 158 to 167 pounds. During the month of March 1947, he had two transient bouts of upper abdominal pain and vomiting. For the most part, his appetite was good and he did not complain of constipation or diarrhea. Early in the morning of July 11, he complained of severe pain in his lower abdomen and nausea. A surgical consultation was held several hours later at which time the abdomen was soft and there was no tenderness. Leucocyte counts made several hours apart were 11,700 and 6,800 per cu mm respectively. Clinical improvement continued and in September the patient was on outside walking exercise and considered ready for discharge.

On October 11 he had another attack of abdominal pain and vomiting, this time the pain was largely in the right upper abdomen. The complaint followed the usual pattern and subsided within a few hours. Following this, the patient was seen by one of us (F G P) in the surgical clinic.

X-ray inspection of the upper gastro intestinal tract (Fig 3) resulted

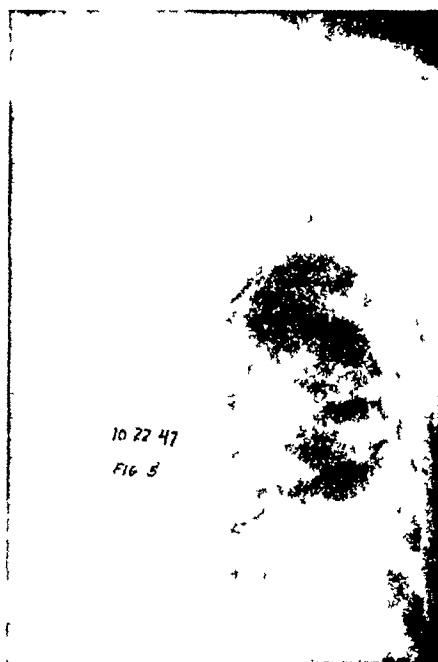


FIGURE 3

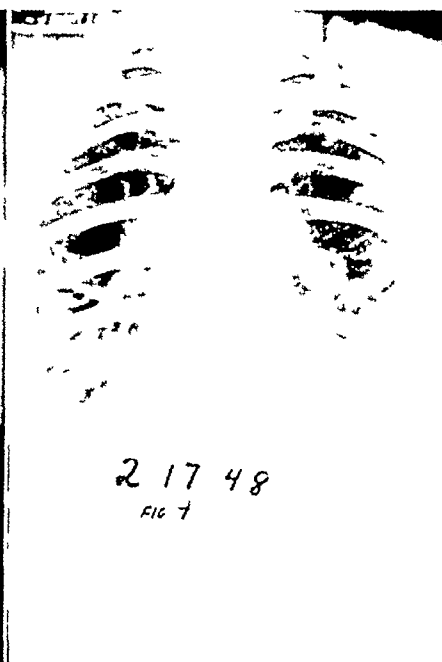


FIGURE 4

Fig 3 Barium x-ray study of upper gastro intestinal tract taken October 22, 1947, revealing the stomach lying high in the left thorax—Fig 4 Roentgenogram taken February 17, 1948, revealing the left diaphragm in normal position and an essentially normal chest.

in a diagnosis of diaphragmatic hernia with all of the stomach and duodenal bulb above the diaphragm

On December 12, 1947, the hernia was repaired by Dr Joseph Robinson, chest surgical consultant Part of the operative note follows "The entire stomach, together with about 12 inches of large bowel and a large amount of omentum were found within the pleural cavity There was a rent in the diaphragm measuring about four inches in length and located just mesial to the dome of the diaphragm It extended in an antero-posterior direction, partially in line with the superior of the two scars in the chest wall The stomach, colon and omentum were diffusely and densely adherent to the ring formed by this tear There was also a small hole in the diaphragm measuring about one centimeter in length and located directly beneath and anterior to the two stab wound scars in the chest wall There was about two inches of omentum protruding through this hole and it also was densely adherent to the edges The lung was entirely free from adhesions The adhesions between the omentum, stomach and large bowel and the edges of the two diaphragmatic herniae were freed by blunt and sharp dissection A small amount of free omentum was resected from the large mass of omentum The bowel, stomach and omentum were then replaced into the peritoneal cavity after controlling a few bleeders following the section of the adhesions The diaphragm was then repaired with 00 silk, using inverted mattress sutures"

The postoperative course was uneventful There was no effusion, and it was not necessary to aspirate air from the pleural cavity X-ray films on December 15, 1947 revealed the left lung to be completely re-expanded with slight pleural reaction at the base

A roentgenogram (Fig 4) was taken February 18, 1948 following which the patient was discharged from the hospital Six months after discharge, he was free from complaints and was leading a normal life

Comment

R Santello² and R Aquilar et al³ describe two cases, one a diaphragmatic hernia of the stomach and the other a congenital hernia in a child, which were erroneously diagnosed as pulmonary tuberculosis Adams and Lee⁴ analyzed the symptomatology of 34 surgically treated cases of diaphragmatic hernia The most common chief complaint was pain in the epigastrium or lower chest which occurred in 23 cases The pain most commonly occurred soon after the ingestion of food or during meals Vomiting often relieved the pain Dyspnea was the second most common complaint and occurred in five patients The remaining common complaints in order were hematemesis, constipation and regurgitation of food The organs most often contained in the herniae of their series were the stomach and colon The symptoms are related to the organs which have been displaced by the hernia Lawrence⁵ quoting from Harrington, refers to diaphragmatic herniae as the "Masquerader of the Upper Abdomen" because the condition is often wrongly diagnosed He describes an auscultatory physical sign "Inspiratory Borborygmi," which made the diagnosis in one

case The sound is only heard when the patient is lying down and is described as a "grunting borborygmus-like sound synchronous with inspiration" The sound is produced by the increased intra-abdominal pressure and the decreased intra-thoracic pressure during inspiration forcing the fluid and gaseous contents into the herniated portion of the stomach H Reid⁶ cites a case of traumatic hernia and discusses the mechanisms by which traumatic herniae may be produced These are direct injury, necrosis of the diaphragm by pressure from a drainage tube or rupture of a subphrenic abscess, and indirect crushing injuries He stresses that such herniae have no sac and therefore are false herniae or eviscerations Kiene and Copleman⁷ describe a right sided hernia with delayed herniation of the liver and gall bladder Numerous authors report the rarity of right-sided herniae Gariepy and Dempster⁸ emphasize the importance of properly using the x-ray to establish the diagnosis of diaphragmatic herniae in which the symptoms may not easily be distinguishable from other diseases of the abdomen or chest They cite examples of patients with massive diaphragmatic herniae who passed from one physician to another without the diagnosis being made They also quote Harrington's report of 161 cases of which 21 had been operated on previously without symptomatic relief and were completely relieved by operation Previous diagnoses in this group included gastric and duodenal ulcer, intestinal obstruction, hyperacidity, heart disease, neoplasm of the esophagus and lung tumor They also quote Hedblom who warns against depending entirely upon the Roentgen Ray for diagnosis since spontaneous reduction of these herniae may occur at any time thus causing them to escape detection It must also be remembered that the herniated omentum and spleen are not seen roentgenologically

Carter and Giuseffi¹⁰ reviewed the literature on 39 cases of strangulated diaphragmatic hernia including two of their own and found a striking repetition of symptoms and physical findings These included a history of a previous thoracic injury, physical findings of displacement of the heart to the right, aspiration of bloody fluid from the left pleural cavity, roentgenologic findings of a high left diaphragm, and signs of acute gastrointestinal obstruction with absence of abdominal distention and a patent intestinal tract where the stomach alone is included All of these criteria were present in our case First, the symptoms were those of intestinal obstruction Second, a penetrating wound in the chest had occurred near the diaphragm This combination of circumstances should have suggested traumatic perforation of the diaphragm and some part of the gastro-intestinal tract caught in the rent of the diaphragm Third, an air-containing space just

above the diaphragm should lead one to consider the possibility of diaphragmatic hernia. Finally, it must be emphasized that in studying these cases the radiologist must be asked specifically to look for a diaphragmatic hernia or the correct examination may not be made. Many of these will be missed unless the patient is placed in a Trendelenburg position at the time the barium studies are made.

SUMMARY

1) A case of traumatic diaphragmatic hernia with two perforations of the diaphragm involving the stomach, transverse colon and omentum is presented.

2) Although definite criteria for suspecting the diagnosis were present, the patient was observed for 11 months in a hospital before the correct diagnosis was made.

3) Clinicians should consider the possibility of diaphragmatic hernia in all cases with obscure symptoms simulating thoracic or abdominal disease.

4) In order that a correct examination will be made, the radiologist should be asked specifically to look for a diaphragmatic hernia.

5) The treatment is surgical.

The authors wish to express their thanks and appreciation to Mr. Thomas Ogden for his assistance in making the photographic reproductions of the x-rays included in this report.

RESUMEN

1) Se refiere un caso de hernia diafragmática con dos perforaciones del diafragma incluyendo el estómago, el colon y el epiploon.

2) Aunque existía una base definida para que se hubiera sospechado el diagnóstico, el enfermo estuvo en observación en un hospital por 11 meses antes de que llegara a un diagnóstico correcto.

3) Los clínicos deben sospechar la hernia diafragmática en todos los casos con síntomas oscuros que simulen un padecimiento abdominal o torácico.

4) Para que un examen sea hecho correctamente, debe pedirse claramente al radiólogo que busque la hernia diafragmática.

5) El tratamiento es quirúrgico.

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Cholesterol Pleural Effusion

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Cholesterol pleural effusion is a rather rare condition. It has been called by several names—cholesterol pleurisy, cholesterol-thorax, cholesterous effusion, and cholesterol pleural effusion, the latter name appears to be the best. It is a pleural effusion with cholesterol crystals in the fluid. Only 44 cases were reported in the literature up to 1929. Since then there have been 15 cases reported. The first detailed description of a case was given by T Churton¹ in 1882. The most recent description was by Curran² in 1948.

The etiology remains rather obscure, but there are many theories concerning its occurrence. The fact remains that although the process of chronic pleural effusions is common, deposits of cholesterol crystals in pleural effusions are rarely encountered.

The following is the case reported.

Chief Complaint H W A, a bookbindery foreman, white, 52 years of age, was admitted on April 7, 1948 with the chief complaint of shortness of breath. Three weeks before admission after walking quite strenuously, there was temperature elevation, rapid pulse and the onset of dyspnea.

A local physician was seen who prescribed treatment for a condition known as Virus "X". After three weeks he was somewhat improved and returned to work, however, he remained short of breath. Because of the persistence of symptoms, he was admitted to the hospital.

Past History Revealed malaria and incipient tuberculosis with sanatorium treatment in 1923. No pneumothorax therapy was instituted. There has been no recurrence of active tuberculosis. In 1938, the patient had bronchiectasis and prostatitis for which he was treated with recovery. In 1940, there was an attack of pneumonia without complications. There were no operations, and no loss of weight or constitutional symptoms.

Family History One daughter had tuberculosis which is now arrested. Mother and father both died of cancer. No nervous or mental diseases.

Physical Examination Revealed an obese white male who was acutely ill. Temperature was 102 degrees F, pulse 120, respiration 45, and blood pressure 175/110. There was dyspnea with mild cyanosis of the lips and nailbeds. The trachea was deviated to the left. There was flatness over the whole right chest with some bronchial breath sounds at the right

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The opinions expressed are those of the author and do not reflect those of the Navy Department or the Naval Service at large.

TABLE 1

BLOOD DETERMINATIONS	1948 — 4-8	4-10	4-12	4-14	4-15	4-16	4-19	4-22	4-27	5-1	5-3	5-7	5-12
Total Protein gms /100 cc									7 43				
Serum Albumin gms /100 cc									4 49				
Serum Globulin gms /100 cc									2 94				
Glucose mgms /100 cc									108				
Cholesterol mgms /100 cc		280											
Cholesterol Esters mgms /100 cc		190											
Urea Nitrogen mgms /100 cc									12 8				
Sedimentation Rate mm /hour			25										12
PLEURAL FLUID													
Specific Gravity	1 030	1 025	1 024	1 022	1 022	1 022	1 020	1 020		1 021			
Total Protein gms /100 cc		5 64									4 05		
Albumin gms /100 cc		3 02									2 5		
Globulin gms /100 cc		2 62									1 55		
Cholesterol mgms /100 cc		721									150		
Cholesterol Esters mgms /100 cc		400											
Bacterial Smear	0	0							0				
AFB Smear	0	0							0				
Bacterial Culture	0	0							0				
AFB Culture	0	0							0				
G P Inoculation		0											
Cholesterol Crystals	+	+	+	+	+	+	+	+	+	+	+	+	+
Amount Aspirated cc	500	2200	1250	650	275	650	250	175	260	225	125	0	0

apex The heart was normal except for rapid rate and accentuated second aortic sound The prostate was boggy and enlarged The remainder of the physical examination was normal The blood count was normal The erythrocytic sedimentation rate was 25 mm /hour Urinalysis revealed only a two plus albuminuria with numerous leucocytes on the microscopic examination The blood urea nitrogen was 12.8 mgms, the serum cholesterol was 280 mgms, and blood sugar was 108 mgms per 100 cc The total proteins were 7.43 gms The serum albumin was 4.49 gms and the serum globulin was 2.94 gms per 100 cc The blood Kahn was negative A thick blood smear did not reveal malarial parasites

Special Studies and Treatment Thoracentesis was done on April 8, 1949, and 500 cc of a yellowish turbid fluid was removed The specific gravity was 1.030 Bacterial and mycobacterium tuberculosis cultures and smears were all negative The pleural fluid revealed many cholesterol crystals and these only

Bronchoscopy done on this day revealed only distortion of the right bronchial tree and displacement of the trachea to the left

On April 10, 1948, a second thoracentesis was done and 2200 cc of opalescent yellow fluid was removed This fluid had a peculiar astringent odor The specific gravity was 1.025 The smears and cultures were again negative, and the smear revealed again only cholesterol crystals The pleural fluid contained a content of 721 mgms per cent of cholesterol and 400 mgms per cent of cholesterol esters, a total protein of 5.64 gms per cent, an albumin content of 3.02 gms per cent and 2.62 gms per cent of globulin Repeated thoracenteses were performed thereafter on April 12, 1948, when 1250 cc of opalescent yellow fluid was removed (On this occasion 10 cc of methylene blue was instilled and was not recovered either in the sputum or on bronchoscopic aspirations) On April 14, 1948, 650 cc of the same type of pleural fluid was removed On April 15, 1948, 275 cc, one day later 650 cc, and three days later 250 cc of yellow, orange fluid were aspirated

During these repeated aspirations the patient regained normal breathing and was ambulatory On April 22, 1948 175 cc of yellow, orange fluid was removed On April 27, 1948 the fluid (260 cc) was straw colored and clear

The next taps were done in May, the first, when 225 cc, and the third, when 125 cc of amber colored fluid were removed

Another bronchoscopy was done on May 3, 1948, when only less distortion of the right bronchial tree was noted

On May 6 1948 fluoroscopic examination revealed only a small amount of fluid covering the diaphragm which remained so until the patient's discharge on May 17, 1948

The fluid revealed cholesterol crystals throughout the hospital stay The laboratory examination of the fluid on May 3 1948, showed total cholesterol 150 mgms per cent and a total protein content of 4.05 mgms per cent with albumin of 2.50 gms per cent and globulin of 1.55 gms per cent There were only cholesterol crystals present The sedimentation rate on May 12 1948, was 12 mm hour The patient was discharged on May 14 1948, and since that time has enjoyed good health He was last examined on March 12, 1949 and was found to have returned to his occupation since discharge and without any symptom or trouble The various data have been tabulated in Table I

Discussion

The rarity of cholesterol pleural effusion is of great interest, especially since chronic pleural effusions are so common. Erwin³ reported that he could only find 30 cases up to 1941, but 44 cases can be found up to 1929, and since 1929, there have been 15 more cases reported in the medical literature. Auerbach⁴ in a large series of approximately 400 autopsy cases of tuberculous empyema and nontuberculous effusion or empyema at Seaview Hospital, Staten Island, New York, could not find a single case in his experience. Durham and Diamond⁵ reported the first case in 26,000 admissions of pulmonary disease cases admitted to the Veteran's Administration Hospital, Oteen, North Carolina. Evander⁶ and Curran² have reported the last cases in the literature.

The reasons that cholesterol crystals form in these fluids have been advanced by several authors. It is always associated, as with this case, with marked pleural thickening. Often, too, the pleural effusion is encysted.¹⁷ However, the gross pressure symptoms noted in the case reported above is a rather uncommon occurrence.

In all cases the characteristic finding is the polyhedral crystals in the pleural fluid. The cholesterol content decreases with the repeated aspirations (as noted in this case).^{2, 7, 11}

An attempt has been made to explain the presence of cholesterol crystals on the albumin-globulin ratio^{7, 12} in which the albumin-globulin ratio equal to, or greater than 1.0 is considered to be cholesterolytic and the cholesterol is thereby kept in solution, whereas, the albumin-globulin ratio less than one, tends to allow precipitation of the cholesterol. Review of the other cases in the literature do not appear to bear out this concept. The case reported in this article does not appear to bear out this view either. It appears that with *in vitro* experiments this influence of the albumin-globulin ratio is true, but it is untrue clinically.

Most of the ideas for the formation of the cholesterol crystals attribute it to local causes, in the main the alterations of the thickened pleura.^{1, 3, 5, 9, 10, 13, 16} There are two workers^{1, 18} who believe that actual lipoidal degeneration of the pleura occurs which forms cholesterol crystals. Coyon¹⁷ believed that most of the cholesterol came from the destruction of the leucocytes in the pleural fluid. Others believe that destruction of tubercle bacilli^{5, 19} or degeneration of caseous foci on the pleura or subpleural zone² results in the formation or spilling out of cholesterol. Barbieri²⁰ holds that the cholesterol originates from the blood and due to pleural alterations cannot be reabsorbed. The views that it is a general metabolic disturbance^{8, 22} do not have any evidence to support them. The local factors associated with the long standing

disease with the marked thickened pleura appear to cause the cholesterol to accumulate due to precipitation of the cholesterol already present. The greatly reduced permeability of the pleura was experimentally shown by Rouillard²²

Although cholesterol pleural effusion usually occurs in middle aged individuals, Sharpe²³ reported a case in a 9 year old child. The question posed by Mainini¹⁹ that the deposition of cholesterol occurs only in the pleural cavity is incorrect, for it has been reported as occurring in the pericardium^{24 25} and peritoneal cavity²⁶

That the condition is closely associated with tuberculosis appears quite evident from the literature and in the case reported in this article, this is true when even the tubercle bacilli are not recovered^{2 6 8 13 15 16 21 27 29}. The highest cholesterol content of pleural fluid reported was 45 grams per litre by Hedestrom³⁰

The treatment of this condition reveals itself into occasional aspirations of the pleural cavity to relieve pressure symptoms, the aspirations should lie between frequent ones and rare ones, and each case will have to be handled individually. One would recommend aspirations every three or four months, which might obviate the development of a bronchopleural fistula. Coyon¹⁷ reported such a complication in one case. This plan of therapy appears to be satisfactory, and in our case the need for further aspirations has not occurred in over one year. It is possible that if the disease is not controlled and is troublesome either due to pressure symptoms or dyspnea or a broncho-pleural fistula, decortication or resection of the lung or both combined may be performed. It is interesting that Chauffard¹¹ recommended a pleurotomy if repeated aspirations were not of value.

SUMMARY

- 1) A case of cholesterol pleural effusion is presented
- 2) The nature, etiology and treatment of the condition are discussed

RESUMEN

- 1) Se presenta un caso de derrame pleural colestéarico
- 2) Se discute la naturaleza, etiología y tratamiento de este estado

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College News

SEMI-ANNUAL MEETING, BOARD OF REGENTS

The semi-annual meeting of the Board of Regents of the College will be held at the Statler Hotel, Washington, D C, on Monday, December 5. The Interim Session of the American Medical Association will be held in Washington, December 6 through 9

NEXT ANNUAL MEETING

The Sixteenth Annual Meeting of the American College of Chest Physicians will be held in San Francisco June 22 through 25, 1950. The Committee on Scientific Program for the 1950 meeting has been organized, consisting of the following physicians:

Herman J Moersch M.D, Rochester Minnesota, Chairman
Osler Abbott, M.D, Atlanta Georgia
Paul H Hollinger, M.D Chicago, Illinois
Edwin R Levine, M.D, Chicago, Illinois
Karl H Pfuetze, M.D, Cannon Falls, Minnesota
Leo G Rigler, M.D, Minneapolis, Minnesota
R H Sundberg, M.D, San Diego, California

Physicians interested in obtaining places on the scientific program are invited to submit titles and abstracts of their material to Dr H J Moersch, Chairman of the committee, Mayo Clinic Rochester, Minnesota

SPECIAL ISSUE OF "DISEASES OF THE CHEST" FOR DECEMBER

The editorial staff of the College journal is preparing a special issue dealing with all phases of chemotherapy and antibiotics in the treatment of diseases of the chest. Articles by the leading authorities in the field will appear in this special issue for December 1949. Additional copies of the special issue will be available and interested physicians are requested to send in their orders early for extra copies.

EXECUTIVE SECRETARY MAKES FIELD TRIP

During an extended field trip, Mr Murray Kornfeld, Executive Secretary of the College, held conferences with the following College officials:

Alfred A Busse, M.D, Jefferson Governor for Wisconsin
Herman J Moersch, M.D, Rochester, Minnesota, Chairman Committee on Scientific Program
Karl H Pfuetze M.D Cannon Falls Governor for Minnesota
Jay Arthur Myers M.D Minneapolis Editor 'Diseases of the Chest'
John F Briggs M.D St Paul President Minnesota Chapter
William A Meyer M.D Senator Governor for South Dakota
Arthur W Dahlstrom M.D Rapid City S D Governor for the Indian Service

William R Rumel, M D , Salt Lake City, Governor for Utah
Ralph G Rigby, M D , Salt Lake City, President, Rocky Mt Chapter
Harold G Trimble, M D , Oakland, California, Chairman, Committee
on Non-Surgical Collapse Therapy
William C Voorsanger, M D , San Francisco, Chairman, Committee on
General Arrangement for Annual Meeting
Seymour M Farber, M D , San Francisco, California, Chairman, Council
on Pan Pacific Affairs
Buford H Wardrip, M D , San Jose, Governor for California
C Gerald Scarborough, M D , San Jose, Secretary, California Chapter
Edward W Hayes, M D , Monrovia, Chairman, Council on Undergrad-
uate Medical Education
William S Conklin, M D , Portland, Governor for Oregon
Florence A Brown, M D , Portland, Secretary, Pacific Northwest Dis-
trict Chapter
Arnold Minnig, M D , Denver, Governor for Colorado
Fred R Harper, M D , Denver, Vice-President, Rocky Mt Chapter
W Bernard Yegge, M D , Denver, Secretary, Rocky Mountain Chapter
Allan Hurst, M D , Denver, Chairman, Committee on Rehabilitation
Max Fleishman, M D , Omaha, Governor for Nebraska
William M Spear, M D , Oakdale, Governor for Iowa

The College program and special activities were discussed with the
above officials

POSTGRADUATE COMMITTEE MEETING

A special meeting was held in St Paul, Minnesota, on Friday evening,
July 15, to discuss the program for the postgraduate course on diseases
of the chest to be sponsored by the Minnesota Chapter of the College in
cooperation with the University of Minnesota. The course will be held on
October 20, 21 and 22, at the Center for Continuation Study on the
Minneapolis campus of the University.

The St Paul members of the College were hosts at the dinner meeting.
Those present were

George N Aagaard, M D , Department of Postgraduate Education,
University of Minnesota
Jay Arthur Myers, M D , Minneapolis, Regent of the College
Karl H Pfuetze, M D , Cannon Falls, Governor for Minnesota
John A Briggs, M D , St Paul, President, Minnesota Chapter
Joseph N Gehlen, M D , St Paul
Clarence Siegel, M D , St Paul
George Wolf, M D , St Paul
Murray Kornfeld, Chicago, Executive Secretary of the College

MEETING OF COLLEGE MEMBERS IN SALT LAKE CITY

The members of the College in Utah assembled for an informal dinner
meeting in Salt Lake City on Wednesday, July 20, as the guests of Dr
William C Walker, and discussed the program of the College. Those
present were

William C Walker, M D
 William R Rumel, M D, Governor for Utah
 Ralph G Rigby, M D President, Rocky Mountain Chapter
 Elmer M Kilpatrick, M D
 Murray Kornfeld, Chicago Executive Secretary of the College

REPORT OF MEETING HELD IN PORTLAND, OREGON

Dr Edward W Hayes, Chairman of the Council on Undergraduate Medical Education of the American College of Chest Physicians, accompanied by Mr Murray Kornfeld, Executive Secretary of the College, arrived in Portland, August 2, and met that evening at the Multnomah Hotel with a group of members of the Pacific Northwest District Chapter and members of the faculty of the University of Oregon Medical School

Dr Hayes talked about the compilation and publication of the book "The Fundamentals of Pulmonary Tuberculosis and Its Complications," which was sponsored by the College and which he was recommending as a text for undergraduates. He also told of the proposed publication of a book covering the non-tuberculous diseases of the chest, including pulmonary manifestations of systemic disease

Those who met with Dr Hayes and Mr Kornfeld were

Dr Charles N Holman Associate Professor of Medicine Administrator and Medical Director of Hospitals and Clinics, University of Oregon Medical School

Dr Hance Haney Associate Professor of Medicine

Dr William S Conklin Assistant Clinical Professor of Medicine and Surgery and Chief of Thoracic Surgery

Dr John E Tuhy Clinical Instructor in Surgery

Dr James T Speros Assistant Clinical Professor of Medicine

Dr Cedric Northrop, Tuberculosis Control Officer, Washington State Health Department

Dr Elton Watkins Jr Resident in Surgery, University of Oregon Medical School Hospitals and Clinics

Dr Florence A Brown Assistant Director Division of Tuberculosis Control

Florence A Brown, M D Secretary-Treasurer
 Pacific Northwest District Chapter

MEETING OF COLLEGE MEMBERS IN SOUTHERN CALIFORNIA

An informal open house and buffet dinner was held at the home of Dr Edward W Hayes in Monrovia California on Wednesday evening August 10. A meeting was held after dinner and Dr Hayes spoke on the undergraduate medical education program of the College. Mr Murray Kornfeld of Chicago Executive Secretary of the College gave a brief talk on the activities of the College. Those present were

C Norman Abbott M D Ontario Antonio Adames M D Holtville
 W A Beck M D Los Angeles Mary Block M D Santa Ana Emil Bogen M D Olive View Harry Brodsky M D Los Angeles Raymond J Cary M D Long Beach William Coughlan M D Los Angeles J R Dravin M D Duarte East M D Duarte T Fred Fujikawa M D Long Beach H Lee Fuller M D Monrovia Otto Glogauer M D Long Beach

Alfred Goldman, M D , Beverly Hills, Edward W Hayes, M D , Monrovia, Edward W Hayes, Jr , M D , Monrovia, F Johnson, M D , Monrovia, William M Kinney, M D , Riverside, Mr Murray Kornfeld, Chicago, E Lundegaard, M D , Orange, W J McKenna, M D , Los Angeles, Solomon Netzer, M D , San Fernando, Jas O'Connor, M D , Los Angeles, F M Pottenger, M D , Monrovia, David Proctor, M D , Pasadena, Paul Quaintance, M D , Los Angeles, Beverly Roberson, M D , Pasadena, J L Robinson, M D , Los Angeles, David Salkin, M D , San Fernando, J J Schmerler, M D , Los Angeles, Marius Seneclick, M D , South Gate, Sidney P Shear, M D , Hollywood, Maurice N Shoor, M D , Duarte, Samuel J Sills, M D , Los Angeles, Jane Skillen, M D , Olive View, R Esmond Smith, M D , Los Angeles, Charles A Smolt, M D , Ventura, Louis I Sokol, M D , Los Angeles, Leo Tepper, M D , Los Angeles, Rollin D Thompson, M D , La Vina, Charles Ware, M D , Pasadena, Waldo Wehrly, M D , Santa Ana, Ruth Wells, M D , Pasadena, and Victor M Yespica, M D , Caracas, Venezuela

COMMITTEE CHAIRMEN MEET IN SAN FRANCISCO

The Chairmen of the local committees for the Sixteenth Annual Meeting of the College, to be held in San Francisco, June 22 through 25, 1950, met at the Bohemian Club in San Francisco on Tuesday evening, August 16. Arrangements for the next annual meeting were discussed. Those present were

William C Voorsanger, M D , San Francisco,
Chairman, Committee on General Arrangements
Edgar Wayburn, M D , San Francisco,
Chairman, Committee on Publicity
Seymour M Farber, M D , San Francisco,
Chairman, Committee on Registration
Harold G Trimble, M D , Oakland,
Chairman, Committee on Round Tables
Sidney Shipman, M D , San Francisco,
Chairman, Committee on Reception
Forrest M Willett, M D , San Francisco,
Chairman, Committee on Housing
Charles Ianne, M D , San Jose,
Chairman, Committee on Fellowship Examinations
Glenroy Piece, M D , San Francisco,
Chairman, Committee on Motion Pictures
William Van Deventer, M D , Redwood City,
Chairman, Committee on Convocation
A Lincoln Brown, M D , San Francisco,
Chairman, Committee on Transportation
J Lloyd Eaton, M D , San Francisco,
Vice-Chairman, Committee on Scientific Assembly
Martin Seid, M D , San Francisco,
Vice-Chairman, Committee on Registration
Buford Wardrip, M D , San Jose,
Vice-Chairman, Committee on X-ray Conference
Murray Kornfeld, Chicago,
Executive Secretary of the College

College Chapter News

MEETING OF ROCKY MOUNTAIN CHAPTER MEMBERS

A meeting of the officers and members of the Rocky Mountain Chapter residing in Denver was held at the Brown Palace Hotel on Friday, August 26. Plans for the annual meeting of the Chapter to be held in Denver on September 20 were discussed. Dr. Fred Harper, Vice-President of the Chapter, presided at the meeting. Those present were:

Arnold Minnig, M.D., Governor for Colorado, W. Bernard Yegge, M.D., Secretary, Rocky Mountain Chapter, Fred Harper, M.D., Vice-President Rocky Mountain Chapter, Maurice Chernyk, M.D., Leroy Elrick, M.D., Allan Hurst, M.D., Sidney H. Dressler, M.D., Major Anibal Valle, Lt. Col. John M. Salzer, Robert C. Cook, M.D., John B. Grow, M.D., John S. Bouslog, M.D., Casper Markel, M.D., Werner S. Prenzlau, M.D., and Murray Kornfeld.

SOUTHERN CHAPTER

The Southern Chapter of the College will hold its annual meeting at the Gibson Hotel, Cincinnati, Ohio, November 13 and 14, in conjunction with the meeting of the Southern Medical Association. The following program will be presented:

Sunday, November 13

2 00 p m — Scientific Session

M. Jay Flipse, M.D., F.C.C.P., Miami, Florida, Chairman, Medical Section, presiding

"Artificial Pneumoperitoneum in the Treatment of Pulmonary Emphysema,"

James J. Calloway, M.D. and Robert H. Furman, M.D., Nashville, Tennessee

"Treatment of Pulmonary Tuberculosis by Streptomycin and Potassium Iodide,"

Hollis E. Johnson, M.D., F.C.C.P., Raymond R. Crowe, M.D., F.C.C.P., Edgar Woody, M.D. and Roy Avery, M.D., Nashville, Tennessee

"Spontaneous Rupture of Esophagus,"

M. Eugene Flipse, M.D., Miami, Florida

Discussion by Osler Abbott, M.D., F.C.C.P., Atlanta, Georgia

"Roll of Bronchoscopy in Pneumothorax Management,"

George R. Hodell, M.D., F.C.C.P., Houston, Texas

6 30 p m — Cocktail Party, Gibson Hotel

7 30 p m — President's Banquet, Gibson Hotel

David H. Waterman, M.D., F.C.C.P., Knoxville, Tennessee, Toastmaster

Presidential Address

Dern B. Cole, M.D., F.C.C.P., Richmond, Virginia

9 00 p m — X-Ray Conference, Gibson Hotel,
M Jay Flipse, M D , F C C P , Miami, Florida, Moderator

Members and guests are invited to bring films to the conference of patients presenting unusual diagnostic problems. Those cases which have been solved will offer the greatest interest and educational value to the membership, and will be called for first in the conference. Unsolved cases on which consultation is desired will follow.

Monday, November 14

9 00 a m — Scientific Session,
Duane Carr, M D , F C C P , Memphis, Tennessee, Chairman, Surgical Section, presiding

"Decortication of the Unexpandable Pneumothorax Lung,"
David H. Waterman, M D , F C C P and Sheldon E. Domm, M D ,
F C C P , Knoxville, Tennessee

"Middle Lobe Disease,"
J. Ray Bryant, M D and John S. Harter, M D , F C C P , Louisville,
Kentucky

"Chest Trauma in Civilian Practice,"
Edward Skinner, M D , Duane Carr, M D , F C C P , Charles
Kessler, M D and W. E. Denman, M D , Memphis, Tennessee

"Acquired Nonmalignant Esophago-tracheobronchial Fistulas,"
Frank Philip Coleman, M D , F C C P and George H. Bunch,
Jr , M D , Richmond, Virginia

12 30 p m — Luncheon Meeting,
Dean B. Cole, M D , F C C P , Richmond, Virginia, President, Southern Chapter, A C C P , presiding

Business Meeting, Southern Chapter

Election of Officers

Guest Speaker's Address

"The Place of Pulmonary Resection in the Treatment of Pulmonary Tuberculosis,"
Norman J. Wilson, M D , Brookline, Massachusetts

George R. Hodell, M D , F C C P , Houston, Texas,
Chairman of luncheon

IX CONGRESS OF U L A S T

The following officers have been elected to preside over the IX Pan American Congress of Tuberculosis Societies, which will take place in Guayaquil, Ecuador, during the latter part of July, 1951

Presidente Dr Jorge A Higgins
Secretario Dr Fernando D Gomez
Secretario General Dr Marco Martinez M
Secretario de Relaciones Exteriores Dr Ernesto Briones
Secretario de Relaciones Interiores Dr Jose Durand N
Secretario de Actas Dr Mayro Madero
Secretario de Propaganda Dr Francisco Marchan
Secretario de Regimen Interno Dr Aurelio Garcia Santos
Tesorero Dr Julio Mata Martinez

URUGUAYAN CHAPTER

The following officers of the Uruguayan Chapter were elected for the year 1949-1950

President Dr Rodolfo Almeida Pintos
Vice-President Dr Frederico Garcia Capurro
Secretary-Treasurer Dr Raul Burgos

The following members of the Chapter presented papers Dr Alejandro Victorica, Dr A Rodriguez, Professor J M Alonso, Dr J C Barani Dr Aristeo Piaggio and Dr Rene Racine

CHILEAN SOCIETY OF TUBERCULOSIS

The following officers of the Chilean Society of Tuberculosis were elected for the year 1949-1950

President Dr Enrique Garcia Suarez
Secretary Dr Hernan Duran M
Treasurer Dr Waldimir Ancich
Directors Dr Cesar Borquez Vial, Dr Enrique Pereda O

College News Notes

Dr Elva Perez-Medina of Havana, Cuba has announced the opening of her office at Edificio Medico, 11th and K Streets Vedado, Havana Dr Perez-Medina will limit her practice to diseases of the chest

Dr Seymour M Farber, San Francisco, California, will lecture on "Contagious Chest Diseases—A Problem in the Practice of Dentistry" and "Recent Advances in Diagnosis and Treatment of Diseases of the Chest" at the Sixth Annual Seminar for the study and practice of dental medicine, Palm Springs, California, October 23 to 28

Dr J J Mendelsohn of Chicago, Illinois left Chicago on August 15th for an extended trip through the following European Countries France, Switzerland and Italy Dr Mendelsohn left on the Queen Mary and will return on the Queen Elizabeth on October 10th

Professor Hector Orrego Puelma, Regent of the College for Chile, presided over the III Postgraduate Course in Tuberculosis given at the Hospital del Salvador, Santiago, Chile The following institutions participated in the postgraduate course Servicio de Tuberculosis del Seguro Obligatorio, Instituto Bacteriologico de Chile Servicio de Cirugia del Hospital de San Jose, Unidad Sanitaria de Quinta Normal, Hospital-Sanatorio "El Peral"

Dr G R Kokatnur of India, recently paid a visit to the Executive Offices of the College in Chicago Dr Kokatnur, a graduate of the University of Minnesota, has been visiting the various medical centers in the United States of America While in Minnesota, he visited with two of his former classmates, Dr Jay Arthur Myers, Editor of *Diseases of the Chest* and Dr Herman J Moersch, Chairman of the Program Committee for the Sixteenth Annual Meeting of the College

MANHATTAN GENERAL HOSPITAL ESTABLISHES TUBERCULOSIS UNIT

The Manhattan General Hospital, New York City, has established a completely isolated tuberculosis unit for the care of 150 patients Dr James S Edlin, Medical Director of the Municipal Sanatorium of the City of New York, Otisville, is Medical Director of the new unit The surgical division is headed by Dr Samuel A Thompson, who is also surgical director of the Municipal Sanatorium

Obituary

SOLOMON BEN ASHER

1894 - 1949

Dr Solomon Ben Asher of Jersey City, New Jersey, died of a heart attack on April 27, 1949 He had a national reputation as a heart specialist and during his lifetime had written many articles on cardiac diseases He was born in Russia in 1894, coming to the United States during childhood, and residing in Jersey City for fifty years He graduated in 1923 from the University and Bellevue Hospital Medical College He was on the cardiology staff of Bellevue Hospital, New York City, and was a Visiting Physician at the Greenville Hospital, Jersey City During World War I, he served with the Chemical Warfare Branch of the Army in Washington, D C

Dr Ben Asher was a member of the International and American Gastro-enterological Associations and an Associate Fellow of the American College of Physicians, as well as a Fellow of the American College of Chest Physicians

He was known as an inspiring and tireless worker by his friends and patients

Irving Willner, M D , Governor for New Jersey

Medical Service Bureau

POSITIONS AVAILABLE

Assistant physician wanted for state tuberculosis institution of 650 beds One with some experience desired Salary \$4,200 to \$4,500 and family maintenance Address Superintendent, Pinecrest Sanitarium, Beckley, West Virginia

Young physician wanted with some experience in diseases of the chest for full time position as assistant to the medical director of a tuberculosis hospital and chest department of a general hospital Please address Box 200A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois

Assistant resident physician with some tuberculosis experience wanted for 225-bed bi-county institution All phases of the diagnosis and treatment of tuberculosis are carried out including major surgery California license required although not immediately Furnished cottage is provided suitable for housekeeping Please outline training and experience in first letter and include a recent snapshot Salary starts at \$450 per month Hospital approved by American Medical Association for training of resident physicians in pulmonary diseases Write Director, Tulare-Kings Counties Joint Tuberculosis Hospital, Springville, California

Wanted—Internist—As Assistant—Mid-West Tuberculosis and Crippled Children's Hospital Recent graduate, Class A school Previous chest experience not necessary Salary open, depending on qualifications No maintenance State starting salary, relevant medical and personal information, and enclose picture with application Please address Box 201A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois

Physician with tuberculosis experience wanted for general hospital and chest clinic California license required Starting salary \$503 per month For further information please write Box 202A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois

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INTERNAL MEDICINE
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Medicine PM 1 — *Physiologic Therapy in Chest Diseases* January 23 to 28, 1950
Fee \$40 Drs A L Barach, H A Bickerman and C Eastlake Monday through Friday, 9 30 - 5 00, Saturday, 9 00 - 12 00

The diseases considered include bronchial asthma, pulmonary emphysema, and fibrosis, bronchitis, bronchiectasis, and pulmonary tuberculosis. The course will consist of discussion of the pathologic physiology of these clinical entities and the application of physiologically directed therapy through lectures and case demonstrations. Recent techniques in physiologic therapy of respiratory disease will be presented including aerosol and inhalational therapy, use of chemotherapeutic and antibiotic drugs, and the immobilizing lung chamber. The method of inducing total lung rest in pulmonary tuberculosis through equalizing alternating pressure will be demonstrated in patients with pulmonary tuberculosis.

BINDING FOR COMPLETED VOLUMES

We are pleased to announce that The Book Shop Bindery, 308 West Randolph Street, Chicago, Illinois, will produce a well-bound volume at as low a price as possible for those members and subscribers who wish to preserve their issues of "Diseases of the Chest." They will bind the six issues of Volume XV in the best grade of washable buckram with gold stamping on the spine and the member's or subscriber's name in gold on the front cover. Please send the six issues to Chicago by express or parcel post prepaid with check or money order for \$2 75 made payable to The Book Shop Bindery. The bound volume will be returned with transportation prepaid by the bindery.

THE BRITISH PHYSICIANS' VIEW OF SOCIALIZED MEDICINE

THE PRACTITIONER, monthly British medical journal founded in 1868 and printed in London, England, has announced an Extra Number—an impartial review of the first year of "The National Health Service Act in Great Britain."

In planning this number, great care was taken to select contributors who are outstanding in their own spheres, who have an intimate knowledge of the working of the Act up to date and, above all, men free so far as possible from prejudice and representing no party or sectional interest.

The Extra Number, containing 110 pages of text, is priced at \$2 00 per copy in the United States of America and Canada. It may be obtained through the *International Practitioner Company*, 12 East 41st Street, New York 17, New York. The date of publication is October 1st, 1949.

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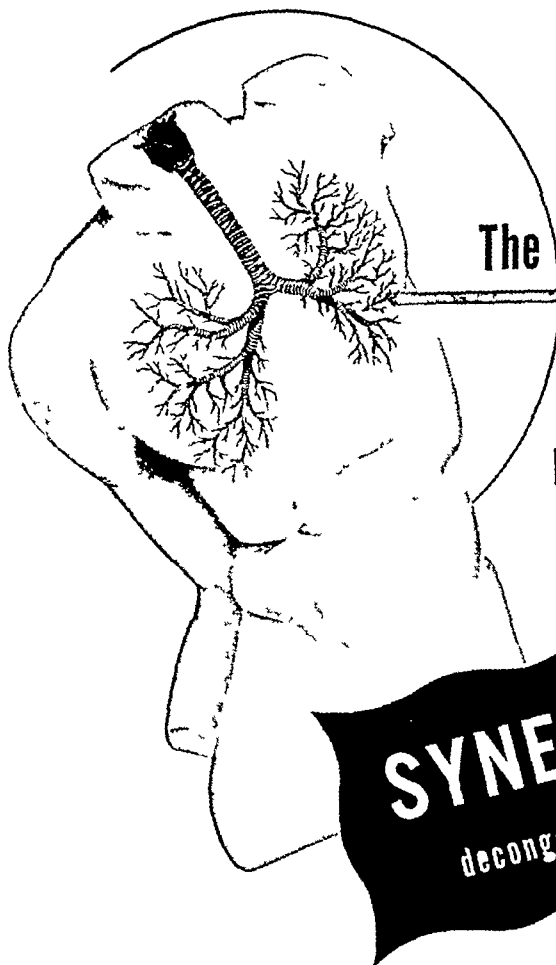
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W N TORRE M.D. Resident Clinician

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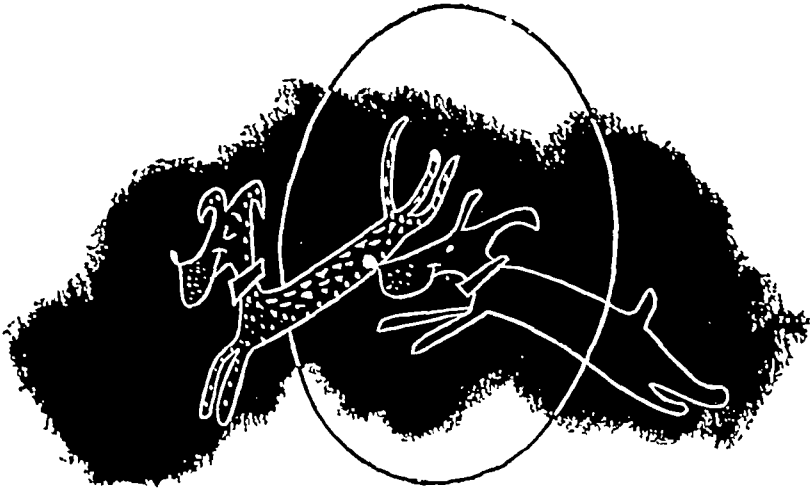
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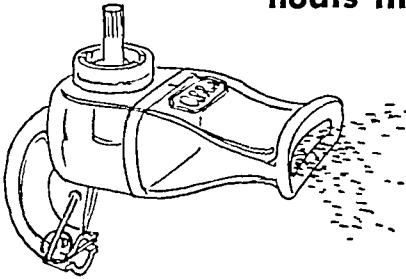
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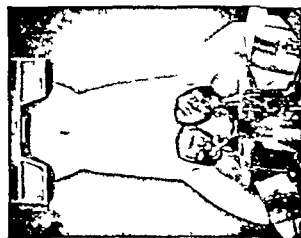
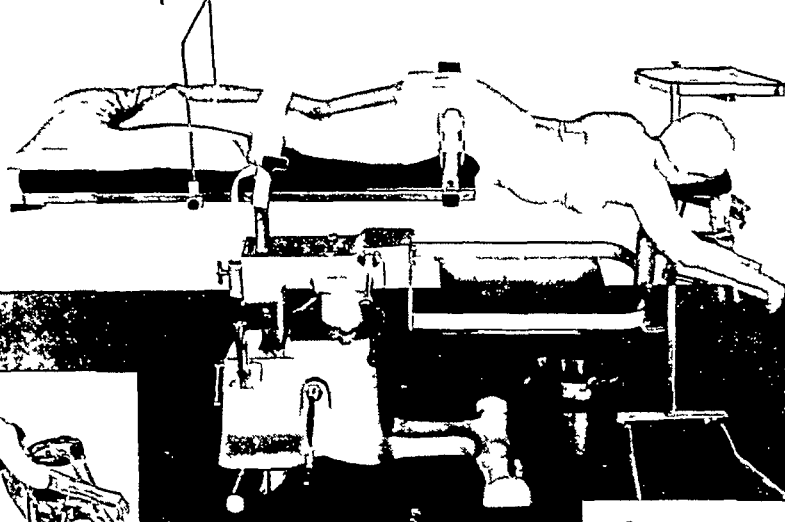
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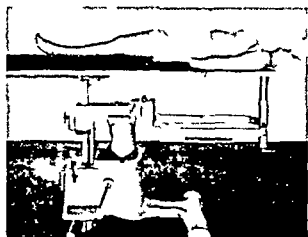
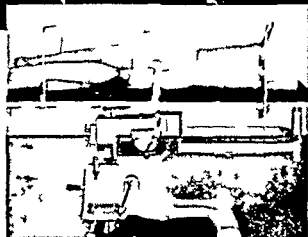


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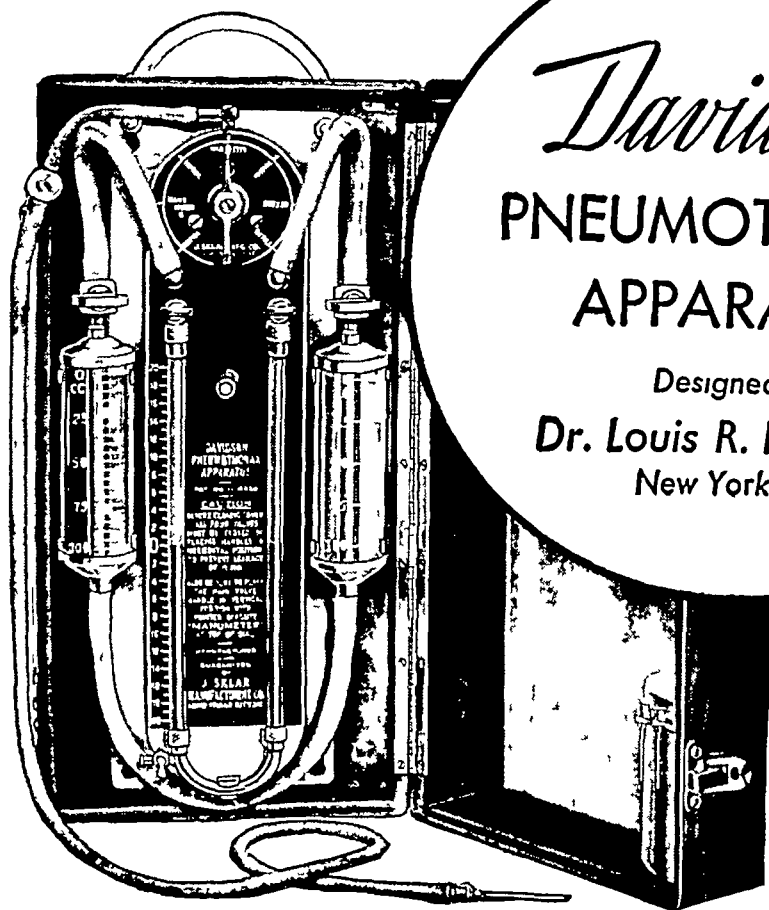


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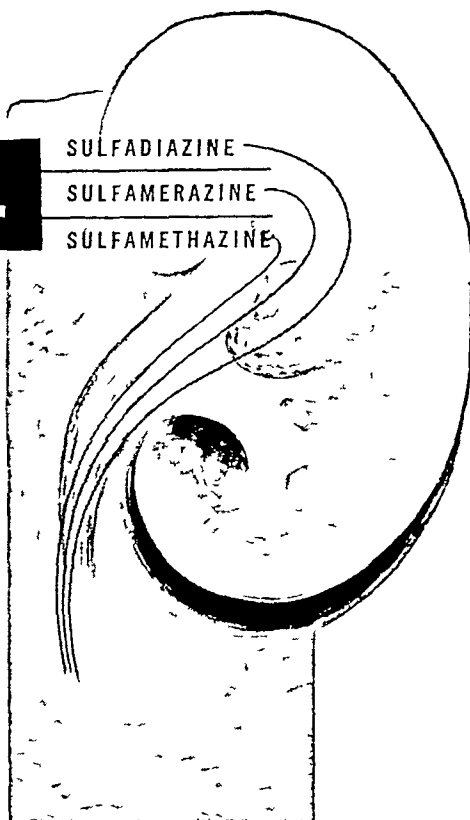
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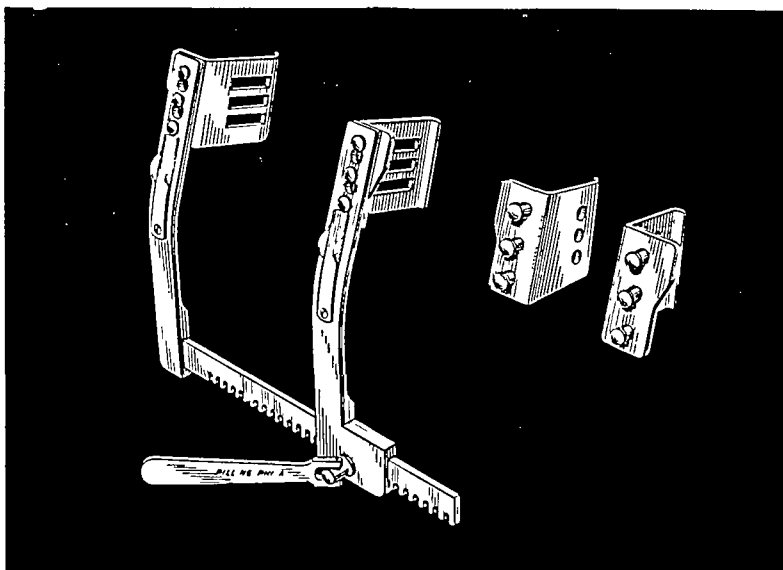


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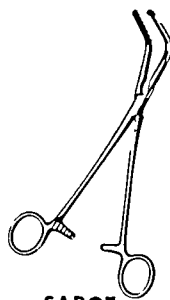
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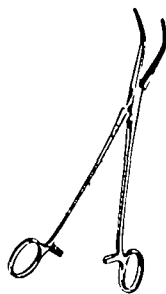
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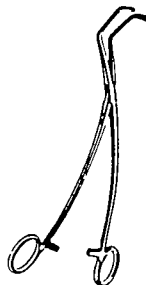
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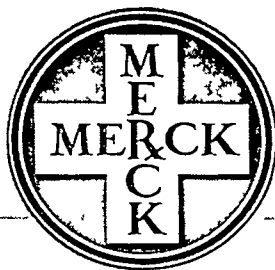
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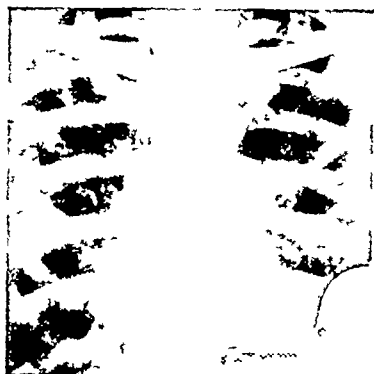


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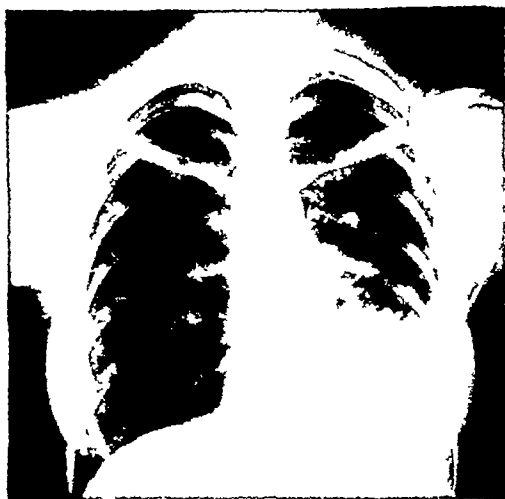
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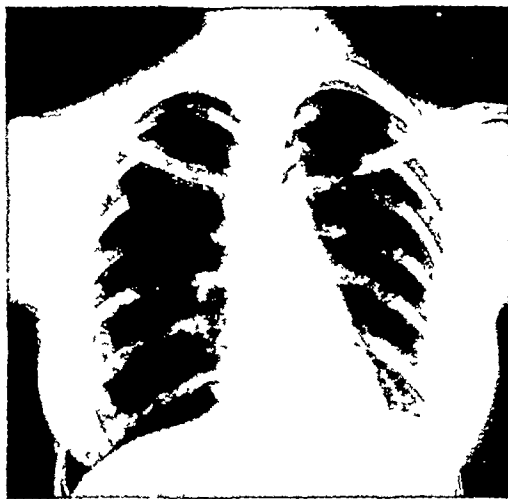
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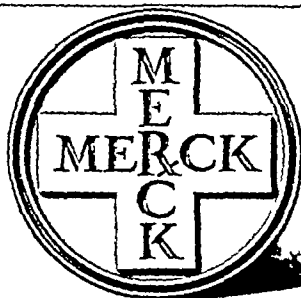


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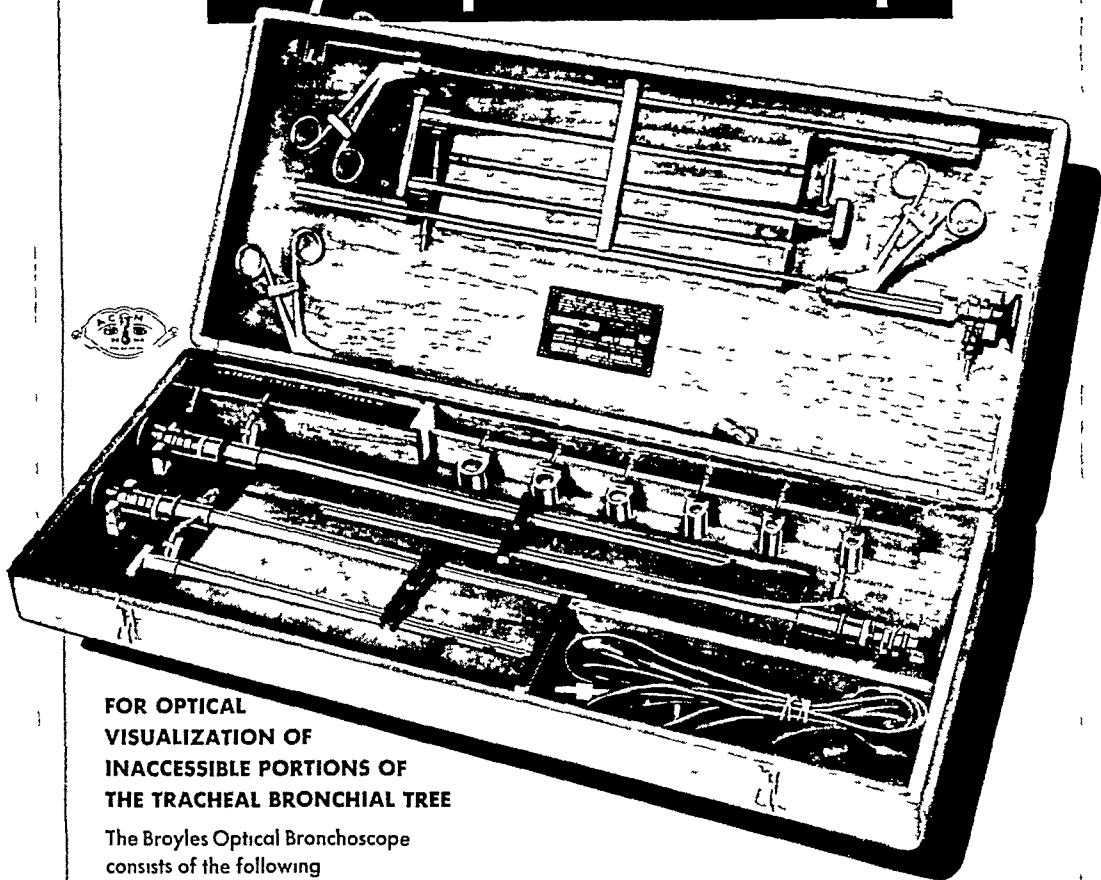
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DISEASES *of the* CHEST

VOLUME XVI

NOVEMBER 1949

NUMBER 5

Closed Pneumonolysis (Enucleation Technique)*

IRVING ARTHUR SAROT, MD, FACS, FCCP
GEORGE FOSTER HERBEN, MD, FACP, FCCP†
and JAMES H. CULLEN, MD, FACP, FCCP††

Yonkers, New York

In 1913, Jacobeus,¹⁷ of Stockholm, first performed closed pneumonolysis. This operation, done through very small incisions with the aid of a telescope, was designed to supplant open pneumonolysis, introduced by Friedrich in 1908. The latter operation, performed through a large incision in the chest wall, had been complicated frequently by pleural infection, hemorrhage, and subsequent obliteration of the pneumothorax space.

Since Jacobeus' original work, many surgeons throughout the world have written of their extensive experiences with this procedure—particularly Gustav Maurer²⁰ in Switzerland, Unverricht³¹ in Germany, Roberts,²⁵ Peter Edwards,¹¹ and Brock⁶ in England, and Alexander,¹ Goorwitch,¹⁴ and Matson¹⁹ in this country. These and other surgeons have, by technical improvements and increasing experience, widened the scope and safety of the operation until at the present time no adequate pneumothorax program can exist without it.

The technique of closed pneumonolysis is difficult to learn because of its endoscopic nature. In the hands of an untrained or inexperienced surgeon it may be the most difficult and, potentially, one of the most dangerous operations to perform properly, requiring infinite patience and attention to detail. There is, therefore, a tendency for some surgeons to deny its value—particularly in cases with extensive adhesions—and to turn rather to thoracoplasty or resection. No one, however, can deny the great value

*From the House of Rest at Sprain Ridge, Yonkers, New York. Presented at the 14th Annual Meeting of the American College of Chest Physicians, Chicago, Illinois, June 18, 1948.

†Physician-in-Chief

††Associate Physician

to the patient of a successful pneumothorax collapse in preference to the more extensive surgical procedures

As the surgeon gains skill, experience, and judgment and progresses from dividing simple string adhesions to operations on more complicated adhesion systems, the results usually improve and the scope of the procedure widens greatly. The safety of the operation in skilled hands from the viewpoint of mortality and complications is gratifying.

Brock quotes Chandler (1935),⁷ "Endoscopic division of pleuro-pulmonary adhesions or internal pneumonolysis would be used more frequently if physicians were convinced that the operation could be performed with safety, that the results were good, that the operation was no ordeal to the patient, that severe reactions need not occur."

Indications for Closed Pneumonolysis In recent years great stress has been laid on the pleural complications and permanent functional crippling of a lung which may attend the continuance of an ineffective pneumothorax, especially if adhesions prevent adequate relaxation and collapse of the diseased portion of the lung while the healthy portions are collapsed. There is general agreement that pneumonolysis is indicated in pneumothorax cases in which cavity closure and sputum conversion are prevented by adhesions. However, opinion is divided regarding this type of intervention in cases in which the cavity has apparently closed and the sputum has become converted but in which there is poor anatomical collapse, with the diseased part of the lung prevented by adhesions from collapsing completely.

Many physicians have by now had the opportunity to observe the end results of pneumothorax therapy with and without pneumonolysis. The general conclusion would seem to be that the so-called "clinically successful" pneumothorax with cavity closure and conversion of sputum despite the presence of adhesions is less likely to yield a permanent good result after cessation of the treatment and expansion of the lung than may be expected in cases in which a complete pneumothorax was obtained with no adhesions or in which all adhesions were severed. The reports of Veran,³² Hurst and Schwartz,¹⁶ and others, all point to the importance of obtaining as complete a release of the lung as possible and contradict the belief that it is sufficient to divide only the "key" adhesions which seem to be preventing cavity closure.

Franz,¹³ in a study of microscopic sections, found unhealed foci of tuberculosis only in those parts of the lung that had been held out by adhesions. From this, Alexander concludes that the localized trauma of respiratory movements upon the lesions is probably the cause of the harmful effect of isolated adhesions.

upon non-cavernous lesions Rafferty,²⁴ finds that "it seems clear that many of the most experienced observers now believe that sputum conversion and apparent cavity closure can no longer be construed as indicating that restraining adhesions are having no harmful effect on parenchymal disease" Andosca and Foley,³ state, "It is our opinion that any adhesions preventing a satisfactory collapse, irrespective of a positive or negative sputum, are an indication for pneumonolysis"

A selective collapse of the diseased portion of the lung should be the object of pneumothorax and pneumonolysis. However, a word of caution must be interjected concerning the division or enucleation of extensive adhesions in a patient whose collapse is clinically successful, with cavity closure and sputum conversion. The limits of safety in any such operation depend upon the skill and experience of the operator. We are cautious when operating upon such a case. However, string and band adhesions and adhesions requiring only a small enucleation should be divided to attain a more selective collapse.

Active lesions in the contralateral lung do not contraindicate closed pneumonolysis provided, according to Alexander, that the lesions are presumably curable with or without collapse therapy. The operation may be done while the other lung is being treated by pneumothorax or after a contralateral thoracoplasty of excision. In our opinion, bilateral cases offer the field of greatest



FIGURE 1a

FIGURE 1b

Fig 1a Extensive bilateral disease August 17 1939

Fig 1b Left pneumothorax with adhesions December 16 1939



FIGURE 1c

FIGURE 1d

FIGURE 1e

Fig 1c Satisfactory collapse on left side after closed pneumonolysis Collapse of right lung hindered by thick columnar apical adhesions August 17, 1940 —*Fig 1d* Satisfactory bilateral collapse March 1, 1941 —*Fig 1e* After voluntary reexpansion of both sides October 2, 1948

applicability of extensive close pneumonolysis, as exemplified in the following case

Case 1 CS, a 19-year-old female, was admitted in June, 1939 with bilateral cavernous tuberculosis (Figure 1a) Left therapeutic pneumothorax was induced in October, 1939 (Figure 1b) A closed pneumonolysis with extensive enucleation was performed in February, 1940 Thoracoscopy was done again in March, 1940 but no adhesions were seen which required division A right pneumothorax was induced, but the sputum remained positive and in August, 1940 (Figure 1c) a right closed pneumonolysis was performed, during which a thick, lung-containing, apico-mediastinal adhesion was enucleated There were no pleural complications on either side and the sputum became negative for tubercle bacilli in June, 1941 (Figure 1d)

Subsequently, both pneumothoraces were continued to May, 1947, when they were voluntarily ended During the period of treatment the patient carried on a moderately restricted but fairly normal mode of life Both lungs reexpanded well after abandonment of the pneumothoraces and the sputum has remained negative (Figure 1e) There is no evidence of active pulmonary disease and the patient is living a normal life

Contraindications to Closed Pneumonolysis Cases of ineffectual pneumothorax may be presented to a surgeon for pneumonolysis which, in his opinion, were not even good candidates for pneumothorax treatment The two main groups into which these cases fall are

- (1) Cases of extensive and wide-spread disease, and
- (2) Cases with a tuberculous stenosis of a major bronchus

In either situation the contraindication to pneumothorax and pneumonolysis lies in the fact that subsequent lung reexpansion may be impossible and that it would have been better to have proceeded at once with a permanent collapse measure such as thoracoplasty, or with pulmonary resection

Almost all cases of therapeutic pneumothorax show, at some time or other in their course, transient pleural effusions Even though diligent search by culture and guinea-pig inoculation may reveal tubercle bacilli in almost all of these fluids, even when clear, they are not considered complications and pneumothorax therapy is continued Many of these fluids will disappear after pneumonolysis However, the appearance of a sizeable pleural effusion requiring repeated tapping, and exhibiting a tendency to recur, should call for a prompt evaluation of the case with a view to abandoning the pneumothorax before a grossly purulent effusion or marked pleural thickening occurs Such complications present themselves most frequently in cases in which the pneumothorax has been maintained despite adhesions which render it incomplete They constitute a strong argument in favor of routine thoracoscopy and pneumonolysis early in the course of

every incomplete pneumothorax Pneumonolysis should not be undertaken when persistent turbid pleural fluid, marked pleural thickening, or evidence of progressive obliterative pleuritis are noted If the formation of pleural fluid, with or without fever, is in the acute phase, operation should be postponed until the acute process has subsided

Tuberculous and mixed-infection empyemata are generally regarded as contraindications, not only to pneumonolysis but also to continuation of pneumothorax therapy

If, at thoracoscopy, a clinically unsuspected acute pleural inflammation is found it is better to avoid pneumonolysis since under such circumstances tuberculous empyema follows frequently The presence of isolated tubercles on the parietal or visceral pleura or at the base of an adhesion is not a contraindication to pneumonolysis, according to Roberts, unless the tubercles are present at the contemplated line of adhesion section The surgeon should use careful judgment in such cases before proceeding, weighing carefully the possible effects of a tuberculous empyema against the absolute necessity of obtaining a collapse in this manner Other collapse or excisional procedures may be preferable

Pleural thickening sufficient to obscure landmarks is a contraindication to division of any but thin cords or sheet adhesions that can be well transilluminated to show they do not contain lung Short adhesions to the chest wall may be enucleated but usually when the pleura is thick an extrapleural cleavage plane is difficult to establish Short adhesions or synechiae at the dome or in the mediastinal area should not be divided when the pleura is thick and the landmarks obliterated because of the danger of damage to the subclavian artery or other large vessel, or the thoracic duct Under such circumstances it usually is better to reexpand the lung and do a thoracoplasty or to proceed at once with excision of the diseased lobe Decortication²⁹ of the remaining lobe or lobes may be necessary to allow them to reexpand to fill the chest cavity

Optimum Time for Operation The optimum time for operation is from eight to 12 weeks after the induction of pneumothorax During this time adhesions will have stretched and in the process will have obliterated many of their intrinsic small vessels It is not advisable to wait longer than three months since the optimum number of cavity closures will have been obtained by then and pleural complications will begin to increase

Maurer has pointed out that immediately following the induction of pneumothorax the pleura is pale, transparent and glistening, and adhesions are easily divided along the line of cleavage in the endothoracic fascia As the pneumothorax proceeds, and

especially if an effusion forms, the pleura becomes dull and thickened, as a result the operation becomes more hazardous. Pushing a pneumothorax to stretch adhesions either before the operation or after an incomplete operation is not recommended.

Operability Once the need for pneumonolysis has become evident, the operability or inoperability of adhesions should not be determined radiologically. It is the usual experience to find at thoracoscopy many more adhesions than are visible on the roentgenograms, and adhesions which on the films seem to be thin sheets or strings may turn out to be the edges of extensive synchia or thick adhesions. Contrariwise, patients in whom one may believe nothing can be done because of most extensive adhesions are found upon thoracoscopy to have a series of thin, overlapping sheets so that what has seemed on x-ray to be an extensive adhesion system is really simple to deal with. Consequently, every patient whose pneumothorax is inadequate or incomplete because of adhesions should be thorascoped in order to obtain the best information. The morbidity from thoracoscopy is so slight that no patient should be denied its advantages.

Despite the fact that many series of good results have been reported, the frequent reference to the complications of empyema and bronchopleural fistula has induced many surgeons to limit their procedure to the division of thin band and string adhesions. Since only a minority of cases (14 per cent²¹) present such adhesions exclusively, a large number of patients fail to have pneumonolysis because the adhesions are short or are seen to contain lung tissue. Failure to divide adhesions in unilateral cases may not be too significant since such patients may go on to thoracoplasty or excision, but a patient with bilateral disease may, under such circumstances, have lost the greatest hope for the arrest of the disease.

In 1930, Gustav Maurer²⁰ published an extensive work on the anatomy of adhesions in pneumothorax. He noted that the configuration of an adhesion is dependent upon the relative degree of fibrosis in the tissues at the parietal pleural attachment and in the adjacent lung, and on this premise he classified adhesions into four main groups recognizable grossly at operation.

- A Cord-like adhesions that show no broadening of either attachment, probably of recent development before the pneumothorax
- B Adhesions with a broadened thoracic wall insertion, they are usually quite fibrotic and less likely to contain lung at the chest wall insertion
- C Adhesions with a conical pulmonary insertion, the broad

pulmonary end always contains elongated pulmonary parenchyma

D Hour-glass shaped adhesions with broadening on both ends

Maurer found that 75 per cent of the 37 adhesions he examined contained lung tissue. When one considers that adhesions usually occur over the most extensive and superficial disease, one should

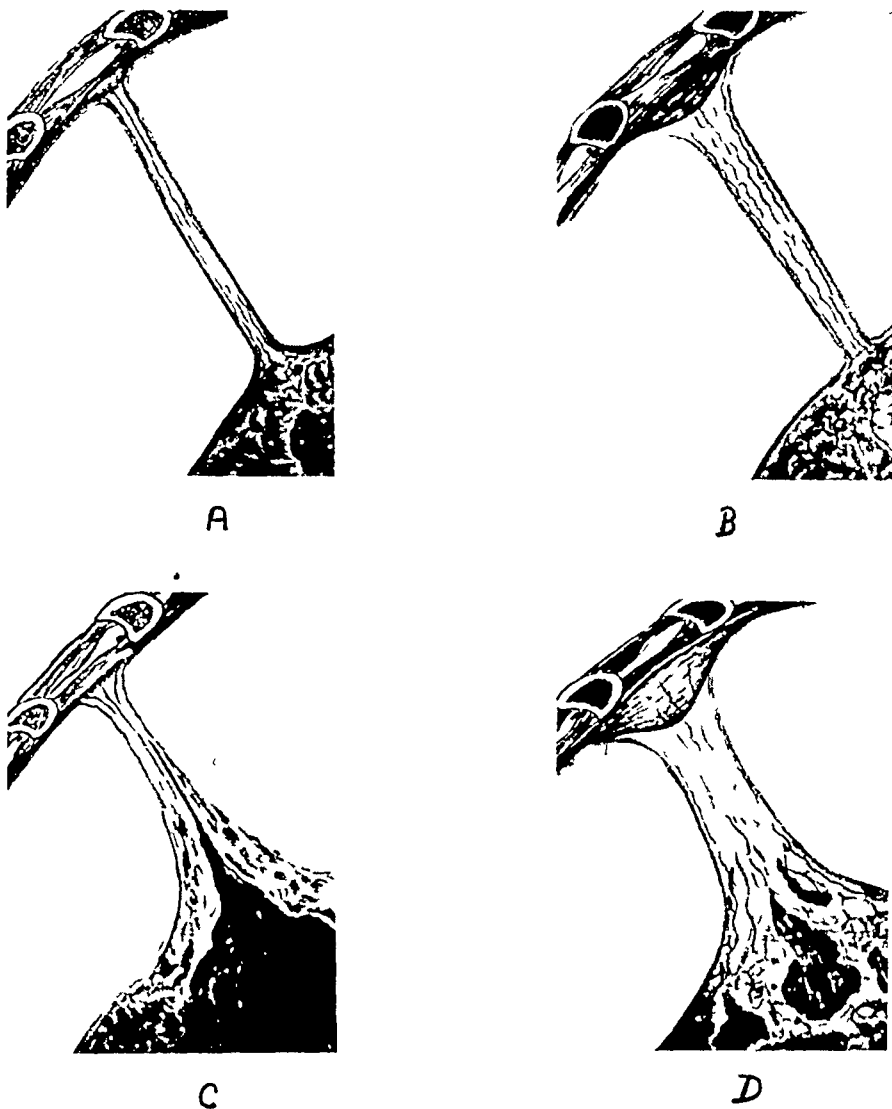


FIGURE 2 (A) "Uniform, formed from connective, especially granulation tissue Lung infiltrated"—(B) "Formed from costal pleura and interpleural connective tissue Lung shows anthracotic scars"—(C) "Formed from interpleural connective tissue and lung parenchyma Lung cavity taking part in it"—(D) "From costal pleura, connective tissue and lung parenchyma, breaking down foci in base of adhesions"—Reproduced from *Thorakoskopie und Kaustik Beiträge zur Klinik der Tuberkulose*, 1930, 76, 9, by courtesy of G Maurer, M D, F C C P

not be surprised to find pulmonary tissue in an adhesion all the way to the thoracic wall Maurer indicated that the usual technique of dividing an adhesion to leave a pulmonary and a pleural stump carried with it inevitably and frequently the complications of hemorrhage, empyema and bronchopleural fistula due to damage to strands of diseased lung tissue traversed by the incision Accordingly, he elaborated his enucleation (or disinserting) technique to provide a means of freeing the adhesion by dissection entirely in the chest wall with consequent lessened danger of damaging the diseased parenchyma since the structure of the adhesion itself is in no way changed Eloesser,¹² in 1924, had employed a similar principle in open pneumonolysis

The adhesion section is carried out under thoracoscopic control in an extrapleural (or endothoracic fascial) plane and the entire freed adhesion retracts into the pleural cavity with the lung Maurer coagulates by diathermy the tissues of the proposed line of incision in the parietal pleura about the base of an adhesion to seal all lymph and blood channels Then by galvanocautery he cuts through the coagulated tissue and so proceeds to enucleate the adhesion Since the coagulation by diathermy causes pain, the operative area is thoroughly injected with procaine by means of a long needle introduced through a cannula and guided under thoracoscopic vision

Instruments When one of us (I A S) first began this work under the personal tutelage of Gustav Maurer and Roberts in 1936, Maurer's instruments were used In subsequent experience we have not found it necessary to have the combined diathermy and galvanocautery administered through the same electrode and con-

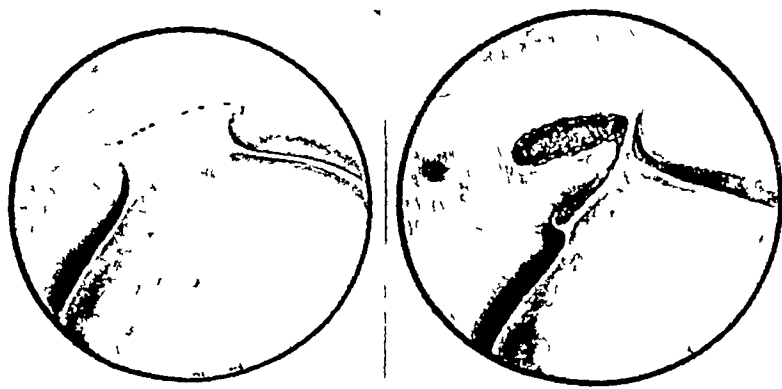


FIGURE 3a

FIGURE 3b

Fig 3a. Enucleation of the adhesion has almost been completed Lung hanging from pleural sheet which is still to be severed—Fig 3b Illustrating the line of incision in the parietal pleura

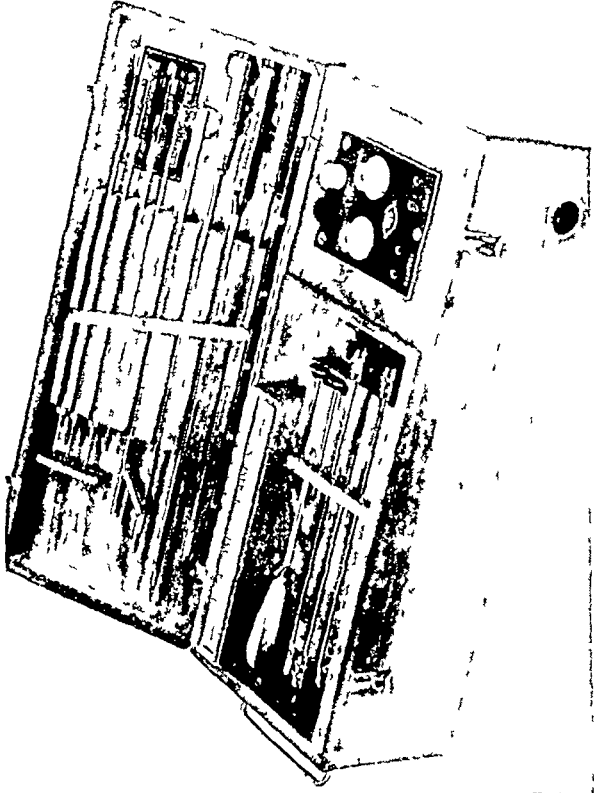


FIGURE 4a

Fig 4a The Thoracoscope in its case

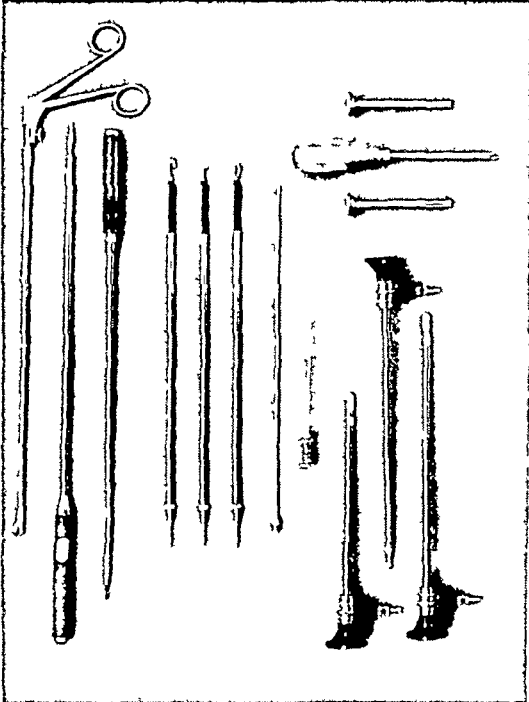


FIGURE 4b

Fig 4b The individual instruments

trolled by a double foot pedal, as designed and used by Maurer. We found that elimination of the diathermy lessened the pain of the operation and internal anesthesia usually was unnecessary. The elimination of the procaine solution at the base of the adhesion facilitated the cutting action of the galvanocautery tip and reduced charring of the tissues. We have never been troubled by bleeding from an adhesion stump and have had no difficulty in controlling by galvanocautery alone any flowing or spurting bleeding points in the chest wall. We prefer the galvanocautery because, with less equipment and expense, it satisfies all our requirements. Matson¹⁹ particularly advocates the use of the high frequency current for cutting, but in addition to the pain associated with this modality, there may be difficulty in regulating the depth of coagulation of the tissue.

When Jacobeus first began to do closed pneumonolysis he used a telescope with right-angle vision through one cannula and introduced the cautery through another one. Following this, Herve (1915) and Mamini (1925) attempted the division of adhesions by means of a cautery introduced through one cannula and guided by fluoroscopic screening, but this was abandoned owing to the danger of uncontrollable hemorrhage and of section of the lung tissue with its sequelae of spontaneous pneumothorax and mixed empyema. In 1918, Morrison Davies suggested the use of a special tenotome which was inserted through the chest wall and the adhesion divided, under fluoroscopic control, by a sawing motion. This method has the same disadvantages as that of Herve.

In the meantime, various operators had suggested telescopes with various angles of vision and finally Davidson (1929), Chandler (1930), and Cutler (1932) devised "single puncture" instruments which carry the cautery and telescope through one somewhat larger cannula. We have used such instruments and have found that their relatively narrow range of movement and lack of flexibility have sharply limited what we were able to accomplish in cases with extensive adhesions.

We prefer a multiple puncture apparatus for several reasons.

First, it is more flexible than a single puncture instrument and adhesion systems can be examined from more than one aspect to decide whether or not they are operable and, if so, how best to proceed,

Second, the cautery and the telescope can be interchanged, when necessary, to afford greater manoeuvrability,

Third, if internal bleeding should occur and the stream of blood should cover the lens system of a single puncture instrument it is bound to be more difficult to control the bleeding than if the

telescope can be removed and reinserted through another puncture hole, and,

Fourth, we cannot subscribe to the desirability of limiting ourselves to just one puncture. In other types of surgery one never hesitates to extend an incision to facilitate the operation and we have never refrained from making two, three, four, or more punctures in the same patient if required to secure an adequate pneumonolysis.

Because of the need for clearer visualization of the operative field, special instruments were designed according to our specifications* which embodied the best features of all previously existing instruments and introduced several new ones²⁶ (Figures 4a and b).

One foroblique vision and two right-angle telescopes are available. The shorter right-angle telescope affords a wider field of vision with a lower magnification and is used for topographic study at the beginning of the operation and for photography. The longer telescope, affording higher magnification of a smaller field, is the so-called "operating" telescope. A correcting prism in the eyepiece yields an erect or non-reversed picture of the interior. This eliminates the difficulty experienced by some surgeons in the use of right-angle-vision telescopes which inverted the image so that the instruments would seem to move in the direction opposite to that intended. Each telescope is supplied with a particularly intense source of light fixed at a short distance from the lens opening. The lens systems are sharply focused and provide a relatively great depth of focus in the field of vision. All air-lens surfaces are "coated" to minimize light reflection and consequent loss of brilliance of the image. We have found these telescopes superior in the visibility which they afford.

Control of the cautery tips by a foot switch permits greater steadiness of the operator's hand. The three variously-shaped platinum tips are thin to minimize burned surfaces. Hook-tip cauteries are used when application of a straight tip is difficult—with them, lax adhesions may be drawn away from the mediastinum or lung into a safe position for cutting. An internal anesthesia needle is supplied, as are biopsy forceps and a suction tube. The suction tube has a guard distally to prevent injury to the lung and the proximal end is "Y" shaped to allow the use of a finger as a valve. A modified Maurer's hook with a finger-tip control in the handle is provided for use as an internal retractor. With it one may draw adhesions aside to see behind them and to investigate the thickness and the pleatings of an adhesion sheet. Two long, locking spongeholders are provided to carry bits of cotton.

*By the American Cystoscope Makers, Inc., whose cooperation is greatly appreciated.

or dental roll for use in dissection in the chest wall cleavage plane or to apply pressure or hemostatics to a small bleeding point

Technique of Operation and Enucleation The lowermost level of the adhesions is determined before operation from roentgenograms and by fluoroscopy. More accurate localization is not necessary. We prefer to use the right-angle vision telescope through a cannula inserted posteriorly to the scapula in the sixth or seventh interspace (Figure 5). The posterior and lateral lung surfaces from apex to base, the paravertebral, posterior, lateral, and, frequently, a good deal of the anterior chest wall from the dome of the pleura to the diaphragm can be inspected easily from this position by rotating the telescope and changing somewhat the angle and depth of its insertion. Inasmuch as the vast majority of pleuropulmonary adhesions in tuberculosis occur over the upper posterior part of the lung (Diehl and Kremer),¹⁰ this approach has been found to give the best field of vision for primary inspection and for the operative work (Figure 6). When necessary, the telescope also can be introduced through the anterior puncture which is usually placed in the third interspace in the posterior axillary line (Figure 5).

With the patient lying on his side and the scapula drawn well forward, skin and soft-tissue anesthesia is induced by injection of about 10 cc. of 1 per cent procaine containing 10 drops of 1-1000 adrenalin chloride to each 30 cc. of solution. The needle is inserted into the pneumothorax, as shown by withdrawal of a small amount

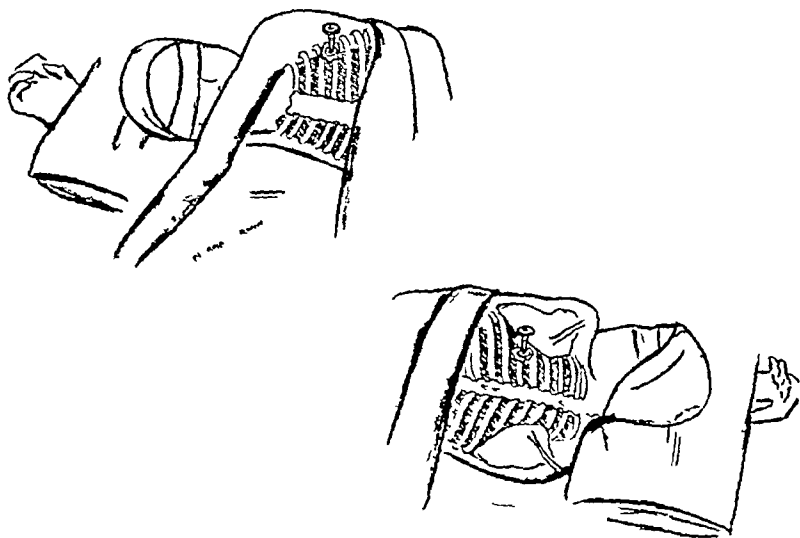


FIGURE 5 The usual sites for the insertion of the cannulae

containing part will usually appear much darker and more opaque. It is important to know that a thin wedge or strand of lung may appear to be transilluminated if a bright light is used. *Consequently, we do not cut through any adhesion unless we can literally see through it.* If the adhesion cannot be sectioned we proceed to enucleate it at its chest wall attachment. The galvanocautery should be used at a dull red heat (as seen in the darkened room) to avoid rapid cutting and bleeding. The parietal pleura is incised by cautery a short distance from a fold of the adhesion insertion. As the pleura is incised the traction of the lung draws the adhesion from the chest wall and a cleavage plane becomes apparent in what is probably the endothoracic fascia. With the high-magnification telescope one can see clearly the fibrous strands of this tissue layer as the pleura is cut at the periphery of the adhesion and the extrapleural dissection proceeds by gentle stripping with a sponge or cold cautery tip.

Tougher strands of fibrous tissue may be cut by cautery. Bleeding points may be controlled by cautery or by pressure with a sponge soaked in adrenalin. Ordinarily there is no bleeding from the lung stump during an enucleation. If a vigorous bleeding point is encountered in the chest wall it is a mistake to attempt to control it by applying a hot cautery tip. This merely results in charring of the blood on the hot cautery. If the cautery is applied cold and the bleeding is stopped by pressure, then application of heat will act to seal the bleeding point. It may be necessary to repeat this manoeuvre several times.

Maurer advocates dissection in the intercostal muscles and rib periosteum when no extrapleural cleavage plane can be found. We did this quite frequently in our earlier cases but more recently have not forced the dissection if no cleavage plane is found. A cleavage plane may be lost momentarily, however, and then recovered by a flanking manoeuvre from another part of the adhesion. Brailon and others have described several cleavage planes in the tissues between the parietal pleura and the intercostal muscles and advocate separation in the outermost plane to avoid dissecting dangerously near the lung. Care should be taken to avoid pulling on the adhesions too vigorously during the stripping. Brock⁶ believes this to be a cause of postoperative vomiting, which may cause trouble in management of the pneumothorax.

We have had occasion to observe these areas of the chest wall from which the lung has been enucleated at various intervals after the operation. Within 48 hours there seems to be present a thin covering-layer of glistening, transparent tissue.

As the dissection is carried in the extrapleural tissue, the parietal pleura is repeatedly incised at the edges until finally the

lung is suspended only by the remaining thin sheet of pleural attachment, which is then divided (Figure 9) If the enucleation has been extensive this pleural sheet may be so slack that the cautery tip cannot be applied to it We have found it helpful to insert another cannula through which a spongeholder or Maurer's hook is used as a retractor to tense the adhesion and to draw it away from adjacent large vessels It is then easy to cut across this remaining pleural sheet to accomplish the complete freeing

If the enucleation has been so large that it becomes difficult to reach the field of operation another cannula may be inserted, at a higher level, to make the approach less awkward If the final freeing can still not be accomplished, it is wiser to discontinue the operation and to wait several weeks, during which time the adhesion retracts and becomes tense again The cannulae can then be inserted in a more favorable location Occasionally a third or fourth stage may be necessary We do not limit a sitting to any specific length of time since it is dangerous to cut the pleural and subpleural fibrous tissue and to leave the lung sus-

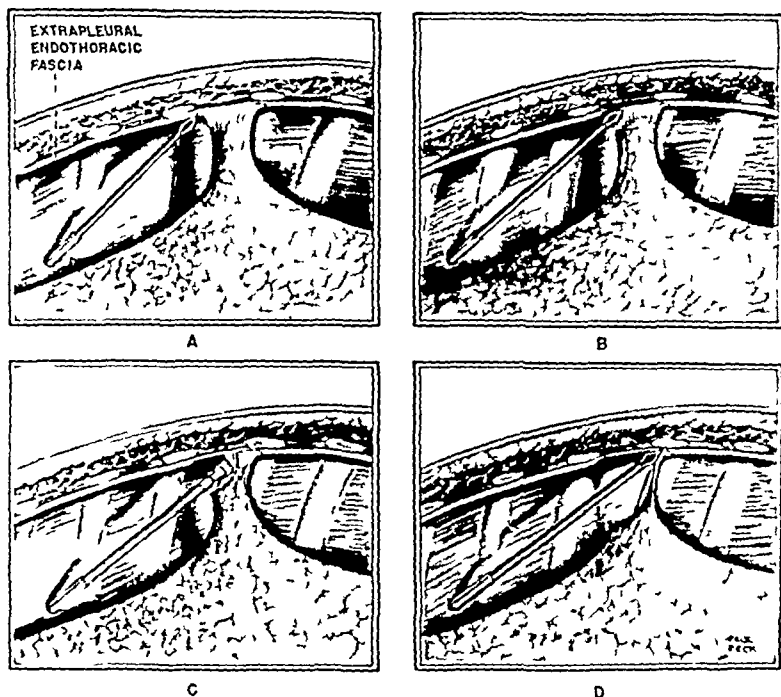


FIGURE 9 (A and B) The parietal pleura is incised by cautery a short distance from the adhesion—(C) The cleavage plane is pursued by sponge dissection—(D) The final sheet of parietal pleura after the adhesion has been dissected from the chest wall

pended on the weakened central diseased core of the adhesion. This may lead to tearing of the lung and empyema. We prefer to prolong the individual operation until enough of the complex adhesion has been dissected from the chest wall to allow the lung to remain suspended from the fibrous sheet at the farther aspect of the adhesion until the next stage.

In a series of 101 cases operated upon by us at the House of Rest at Sprain Ridge, Yonkers, New York, during the past 10 years, the operative procedures were divided as follows:

TOTAL NUMBER OF PATIENTS	101
TOTAL OPERATIVE PROCEDURES	120
Thoracoscopy	7
Pneumonolysis,	
One stage	78
Two stages	13
Three stages	3

We believe that all adhesions that can be divided, should be, and do not attempt to cut so-called "key" adhesions only—we cut the adhesions first that are most accessible. Some surgeons advocate cutting all the fine adhesions first, believing that sudden tension on them after a large adhesion has been cut may lead to their tearing with consequent empyema. We have not seen this happen.

Adhesions may be so located as to render section dangerous. The most frequent site for such dangerous location is at the apex over the subclavian vessels. If the adhesions are long and can be determined by inspection and transillumination not to contain lung they may be cut across—preferably at least one centimeter from the vessels. If the adhesions are short and thick they cannot be cut but may be enucleated from this area. The incision through the parietal pleura and the establishment of the cleavage plane must be done at a good distance from the vessels—perhaps even at some distance from the adhesion. The pleural sheets must be stripped to be quite long so that their division by cautery may be done at least one centimeter from the vessels. It is at this point that it is very useful to insert another cannula through which a spongeholder may be used as a retractor. We have done many such apico-mediastinal enucleations, especially in bilateral cases, as has Brailon⁴ and also Michetti (quoted by Brailon). Naturally a great deal of experience and exquisite care and patience are required in these cases.

Case 2 W B was admitted in September, 1940 (Figure 10a). Shortly thereafter a left therapeutic pneumothorax was induced and extensive apico-mediastinal adhesions were noted (Figure 10b). Six weeks later a

pneumonolysis was performed, during which an extensive apico-medias-tinal extrapleural enucleation was done. After the lung and adhesion had been stripped from the region of the subclavian artery for several inches, the remaining mediastinal attachment was too lax to permit further division. The tension cavity (Figure 10c) closed slowly and in January, 1941, the mediastinal sheet adhesion, which had retracted, was cut in a second-stage pneumonolysis to permit final cavity closure. The sputum became negative in August, 1941 (Figure 10d), and the pneumothorax was continued uneventfully to voluntary abandonment in April, 1945. The lung reexpanded, with moderate pleural thickening (Figure 10e), and the patient has remained well and working.

We have not enucleated adhesions from the pericardium nor from the diaphragm.

The presence of a cavity, superficially placed and near the adhesion, is an indication for caution. Conant and Dale⁸ advise against cutting adhesions in such cases because part of the blood supply to the outer wall of the cavity may come from the parietes through the adhesion. They believe that interference with the blood supply may cause necrosis of the cavity wall. If a cavitated area of the lung is directly adherent to the chest wall we would not attempt to do a pneumonolysis. But we have learned that roentgenograms may be misleading in the determination of the relationship of the cavity and the adhesion. Thoracoscopic examination may reveal that the cavity is actually separate from the parietal wall and the adhesion may be enucleated safely and easily.

"Tension" cavities are regarded by most surgeons as a contra-



FIGURE 10a

FIGURE 10b

Fig 10a Condition on admission September 7, 1940—Fig 10b Pneumothorax collapse hampered by extensive adhesions October 5, 1940



FIGURE 10c

Fig 10c After first stage pneumonolysis Rounded cavity visible October 19, 1940

Fig 10d Cavity closed after second pneumonolysis November 18, 1941

Fig 10e Lung reexpanded Patient well August 10, 1948

FIGURE 10d

FIGURE 10e

indication to pneumonolysis because, after release of the adhesion, unless the bronchus becomes completely occluded due to change in position and direction, the valvular mechanism in the bronchus may permit the cavity to balloon and possibly to rupture. The fact that a cavity is rounded in appearance, roentgenologically, is not sufficient basis for a diagnosis of tension cavity (Figure 10c). Also, many cavities may fluctuate in size without being true tension cavities. Our experience has been that more round cavities will close than will balloon after pneumonolysis.

Case 3 L W, male, 23 years old, was admitted in January, 1940, with a small cavity in the apex of the right upper lobe and positive sputum. Right pneumothorax was induced promptly and, despite apical adhesions, the cavity closed and sputum became negative after three months.

In November, 1941, the sputum became positive again and a new cavity was found in the inferior lateral portion of the right upper lobe (Figure 11a). This rounded cavity fluctuated in size. The apical adhesions, although not over this cavity, were considered to be hindering the collapse. A closed pneumonolysis was performed (November, 1941) and several posterior apical adhesions were enucleated. The cavity fluctuated in size for several months, occasionally "ballooning" to a marked degree (Figure 11b), but finally closed in May, 1942, the sputum becoming negative for tubercle bacilli (Figure 11c). Subsequent cavitory disease in the left lung was treated successfully (1943-1947) by a pneumothorax uncomplicated by adhesions. The right pneumothorax was abandoned voluntarily and now both lungs are well reexpanded and the patient is a hard-working business executive (Figure 11d).

Inasmuch as tension cavities do not do too well under thoracoplasty and since resection can be done if a cavity balloons after pneumonolysis, we believe closed pneumonolysis should be undertaken in such cases.

The operability in each case depends on the experience, skill and judgment of the surgeon. The enucleation technique has widened greatly the scope of closed pneumonolysis. Nevertheless, in all cases in which an extensive enucleation (more than two to three inches in diameter) is necessary, the patient's clinical condition and the status of the contralateral lung must be carefully assessed. In unilateral cases it may be wiser to proceed with a thoracoplasty or excision.

Preoperative Preparation The preoperative preparation consists largely of the pneumothorax therapy. It is unnecessary to push the pneumothorax to positive pressures in anticipation of the pneumonolysis and it is likewise unnecessary to give a large refill of air just prior to operation.

The chest and axilla are prepared as for any surgical procedure. For preoperative sedation we prefer to give three grains of a rapidly-acting barbiturate such as nembutal or seconal about two hours before the operation and then one-quarter grain of mor-

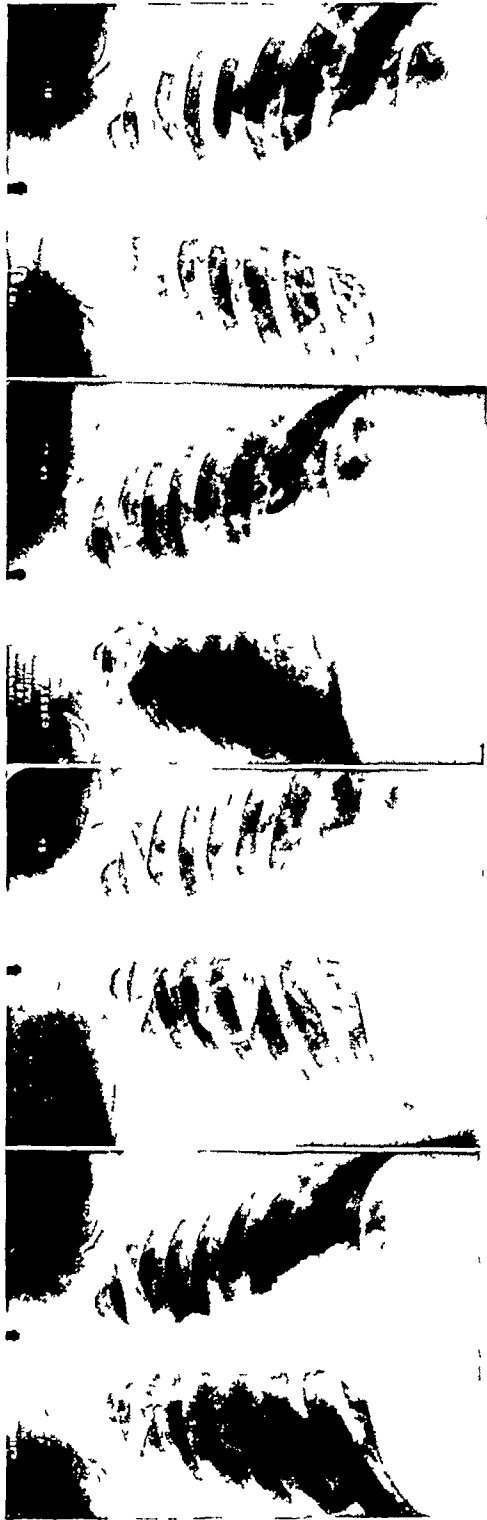


FIGURE 11a

FIGURE 11b

FIGURE 11c

FIGURE 11d

Fig 11a Tension cavity, right upper lobe November 15, 1941—*Fig 11b* Cavity "ballooned" January 24 1942—*Fig 11c* Right lung well collapsed, tension cavity closed Suspicious disease area in left upper lobe March 22, 1943 —*Fig 11d* Both lungs reexpanded Patient well

phine and one-one hundred fiftieth of a grain of scopolamine or atropine about 30 to 40 minutes before operation

Conduct of Operation The operation should be done in a darkened operating room. Full surgical asepsis must be observed and a set of instruments for thoracotomy must have been prepared and be available at an instant's notice. No pneumonolysis should be undertaken unless at least one member of the operating staff is capable of immediately opening the chest surgically to stop bleeding if an accident should occur. Fortunately, such a need is rare. We have never yet had to do this. Alexander and others have described the occurrence of massive hemorrhages due to accidental damage to a large vessel. Thoracotomy must be prompt to save the patient's life.

The instruments should be boiled adequately except for the telescopes which are immersed for 20 to 30 minutes in a non-alcoholic antiseptic solution. Inasmuch as condensation will occur on a cold instrument when it is subjected to body temperature, a small basin of hot water should be provided on the instrument tray to warm the surface of the instrument before its introduction into the chest cavity.

Anesthesia Local anesthesia is preferred for several reasons. Most anesthetists will hesitate to administer a general anesthetic when diathermy or cautery is to be used. Respirations and lung movement are more easily controlled with the patient awake. As the lung collapses when the adhesions are cut it is of great advantage if the patient can expectorate the accumulated secretions.

In addition to the skin and chest-wall infiltration with procaine, Maurer anesthetizes the chest wall internally about the adhesion and occasionally the intercostal nerves medially. With galvano-cautery this is not usually necessary even when extensive enucleations are performed. The patient experiences more pain from the traction on an adhesion than from the heat of the cautery.

Position on Table Special tables and positions are not necessary. We have come to prefer the insertion of an additional cannula and a retractor to attempts to shift the position of the lung and the course of the adhesion by posture. When the patient lies on his side, several folded sheets under the lower ribs will help to make the uppermost side convex and so widen the intercostal spaces. If telescopes of other than right-angle vision are employed, the patient must be positioned differently since the puncture sites will be differently located.

Dyspnea may be troublesome during the operation, especially in bilateral cases. If a pneumothorax needle (Saugmann) is inserted into the pleura through an intercostal space and gentle suction attached, the dyspnea will usually be relieved. Roberts

suggests the use of an aneroid pressure valve in the system to keep the suction pressure about -2 cm of water

Blood is an irritant to the pleura and at the conclusion of the operation it is our custom to aspirate all blood and clots and to lavage the pleural cavity with a liter of warm saline solution, which is then aspirated through the suction tube. The puncture holes are inspected from within the chest by the thoracoscope to determine whether any bleeding persists. We remove the anterior cannula first and watch the internal orifice of the puncture site carefully for a short time because, in our experience, most of the postoperative bleeding has come from this puncture. The intercostal vessels lie more exposed in the intercostal space anteriorly and are more likely to be damaged. On several occasions we have noted roentgen shadows on the anterior parietal pleura below the puncture hole and thoracoscopic examination has revealed these shadows to be due to blood clotting on the chest wall as it trickled from the puncture hole. If bleeding is seen when the cannula has been removed, we employ Overholt's manoeuvre²³ of dissecting a bit of muscle from the tissue about the incision and, after putting a catgut ligature about it, dropping this muscle plug through the re-introduced cannula. After the cannula is removed the second time the muscle plug is drawn up into the chest wall by the ligature and secured by tying the catgut over a cotton roll.

When the patient lies on his side the mediastinum swings toward the dependent side. If the cannula is extracted and the chest is closed while this condition exists, the mediastinum will tend to swing back to the mid-line when the patient changes position and the inordinately large amount of air trapped in the chest will cause a temporarily higher pleural pressure and lead to more marked postoperative subcutaneous emphysema. Therefore, the remaining cannula is removed during expiration.

The skin incisions are closed by silk sutures and a fairly tight compression dressing is applied to prevent, as much as possible, the escape of intrapleural air into the subcutaneous and subfascial planes of the chest wall.

Postoperative Care Fluoroscopy is performed immediately after the operation and again the same evening if the operation has been done early in the day. The patient can usually sit up on a stretcher before the fluoroscope with little discomfort. If a refill or aspiration of air is seen to be required, the adjustment with final negative pressures is made at once. The patient is fluoroscoped and the pressures adjusted the next morning and then at least every other day until the pneumothorax is again stabilized. Failure to fluoroscope the patient frequently enough to observe fluid accumulation and the position of the lung may result

in loss of the pneumothorax by readherence of the lung The lung should be kept well down for several weeks after pneumonolysis to permit complete retraction of the adhesion stumps

Accumulated intrapleural fluid is aspirated promptly and at frequent intervals thereafter Blood is a pleural irritant and aspiration of fluid is a safeguard against fibrin formation at the base causing reexpansion of the lung Maurer, Diehl and Kremer, and Roberts, all stress the fact that the presence of blood in the pleural cavity seems to increase the incidence of tuberculous empyema

The position of the patient in bed is important Most surgeons keep the upper part of the body elevated to allow the fluid to gravitate to the base In addition, we keep the patient lying on the unoperated side, almost prone, for at least 72 hours so that the lung may be kept as much as possible away from the operated area posteriorly Of course, if the site of the operation has been anterior, the patient lies supine

Sedation should be directed largely to suppressing violent cough Pain is usually mild after pneumonolysis and the bad effect of interference with the cough reflex with retention of secretions must be borne in mind Codeine in moderate doses is usually prescribed

Patients who have previously been ambulatory are kept in bed until the pneumothorax is stabilized, fever has subsided and fluid has ceased to accumulate—generally about a week If fluid accumulates and fever persists, especially if associated with evidences of beginning pleural thickening, the pneumothorax should, usually, be abandoned and rapid reexpansion of the lung encouraged Oxygen lavages may be of help

Despite complete anatomical collapse of the lung, cavities may fail to close because of thick walls that resist collapse, failure to obtain complete bronchial occlusion, or progressive excavation of the lung If the cavity does not close after three, and certainly after six months, and if the case is otherwise suitable, a resection or thoracoplasty should usually be considered If lobectomy or pneumonectomy is decided upon, the operation should be performed without abandoning the pneumothorax We have seen severe spreads of the disease during the period of reexpansion of the lung If thoracoplasty is decided upon, to obtain the best results the lung must be reexpanded completely, as soon as possible, before proceeding

If the collapse by pneumothorax has been complete, or at least seemingly adequate, we have considered that thoracoplasty will not afford a greater degree of collapse and recently have preferred to proceed with resection This is especially true in cases in which

the visceral pleura has become somewhat thickened so that complete reexpansion of the lung may be difficult, since the almost-universal experience has been that thoracoplasty over a partial pneumothorax has yielded relatively poor results in cavity closure. If lobectomy is performed, we can, if necessary, decorticate²⁹ the remaining lobe or lobes of the lung and favor rapid reexpansion by controlled suction intercostal drainage. Streptomycin is given during the immediate pre- and postoperative period.

Complications The more common complications following closed pneumonolysis are surgical emphysema, hemorrhage, readherence of the lung, spontaneous pneumothorax, and empyema with or without bronchopleural fistula. Surgical emphysema occurs to a variable degree in almost every case but is not a serious complication in itself though it may be uncomfortable for the patient.

Hemorrhage may be a severe complication. The accumulation of blood or bloody fluid in amounts over 250 cc which require several tapplings should certainly be considered a hemorrhage. We have not seen bleeding from an adhesion stump, we have found that it usually comes from a cannula puncture site. It is important to know that when sizable bleeding occurs after pneumonolysis the clinical picture is that of shock from blood loss long before any evidences of tension pneumothorax appear. Even in cases of severe bleeding, thoracotomy usually fails to reveal the bleeding point. It is usually preferable to give supportive transfusions and to aspirate the pleural fluid as frequently as necessary.

Blood may clot in the pleura and lead to readherence of the lung. Occasionally it is desirable to thoracoscope the patient again to break up the clots with the suction tube and to aspirate them after lavaging the pleural cavity with warm saline solution. It may be possible by so doing to restore a good pneumothorax. However, bloody fluid in amounts large enough to require tapping may continue to appear for several weeks, slowly becoming clear and finally disappearing.

Readhesion of the lung to parietes, with loss of effective pulmonary collapse is an infrequent but serious complication of closed pneumonolysis. Maxwell²² has pointed out three forms of this complication.

(1) The acute obliteration which usually develops within 48 hours of operation and is often total. It is generally considered a sequel to lung reexpansion as a result of massive escape of air from the pleural cavity in the presence of pleural changes that lead to rapid adherence of the visceral and parietal surfaces. Pulmonary emphysema, severe postoperative coughing or vomiting, and inadequate closure of trocar puncture sites are regarded as the chief causes of lung reexpansion.

Brantigan, et al,⁵ have described cases which suggest that endobronchial tuberculosis may be a factor, by producing, after pneumonolysis, a check-valve type of bronchial obstruction that results in rapid reexpansion of the lung and loss of a pneumothorax space

(2) Secondary obliteration occurs within a week or two of operation and tends to be more localized than the first variety, the sites of predilection being the posterior mediastinum, the paravertebral gutter, and the area of posterior chest wall between rib angles and posterior axillary line referred to endoscopically as the scapular zone. The occurrence of a readhesion of the lung is readily noted fluoroscopically. The lung is less mobile and there is usually a line suggestive of pleural thickening at the lung edge. This may be seen endoscopically to be a thin layer of blood clot. Divided adhesion surfaces alone or in conjunction with previously intact pleural surfaces may be involved. Faulty postoperative posture, inadequate control of the pneumothorax postoperatively, or a combination of both, are the important causal factors.

(3) Late obliteration is nearly always a sequel to postoperative effusion or to poor management of the pneumothorax with inadequate refills.

From the literature, Maxwell has found that acute reexpansion and readhesion of the lung (Classes 1 and 2) is reported to occur in about 13 per cent of cases, but, in addition, he comments that the great majority of cases are not recorded and that minor degrees of readhesion are not noted — as a consequence the condition seems much more rare than it actually is. It is stressed that careful attention to the details of postoperative care will usually prevent this complication.

Maxwell reported six cases in which prompt operative intervention reestablished a good pneumothorax collapse. In only one case, one in which pleural tuberculosis existed before "lysis," did tuberculous empyema supervene.

A small pleural effusion frequently occurs after pneumonolysis in at least one-half the cases. This, if of no consequence, clears up in a few days and is most likely due to the reaction of the pleura to the burn and to the blood. Occasionally, cases that develop simple effusions do not settle down but continue to have fever for some weeks, later the effusion becomes turbid and then a frank empyema. Goorwitch believes that the great majority of complications attributable to pneumonolysis occur in the first four weeks after operation. We customarily group as "postoperative" all pleural complications which occur within three months after the "lysis."

From the reports in the literature, the total incidence of empy-

emas (tuberculous and mixed) would seem to be from 10 to 25 per cent This has not been our experience, nor that of Maurer or Brock We believe this discrepancy is due to the fact that these surgeons prefer to enucleate adhesions Brock reports that in 360 operations he incurred much or persistent fluid in 22 per cent, tuberculous empyema in 14 per cent, and mixed empyemas in 14 per cent, for a total of 5 per cent Stetzbacher (1947)³⁰ mentions that Maurer has operated upon 2000 cases In his first 160 cases he incurred only two tuberculous empyemas In the 85 cases operated during the time Stetzbacher observed Maurer's work, the only complications were instances of slight transient fluids, and no empyemas nor hemorrhages In our 10-year series at the House of Rest, the complications were as follows

Complications in 120 Operations on 101 Patients

	Cases	Per cent
Serosanguinous fluid	17	16.8
Transient serous fluid	12	11.9
Purulent tuberculous fluid	5	4.9
Bronchopleural fistula	0	0
Mixed-infection empyema	0	0

Persistent clear effusions that complicated the pneumothorax are classed with purulent tuberculous fluids Therefore, we believe that Maurer's enucleation technique not only increases the number of cases which can be operated successfully but also significantly reduces the incidence of empyema In the five cases in this series with persistent tuberculous fluid, the lungs were promptly and rapidly reexpanded and the pleural space obliterated Successful thoracoplasties were then performed One of the worst mistakes in judgment, if the patient is fit to undergo further surgery, is the maintenance of pneumothorax complicated by tuberculous fluid following pneumonolysis

If tuberculous empyema persists over a controlled lung, a thoracoplasty may be indicated, with or without preliminary thoracotomy drainage Decortication, as advised by Gurd,¹⁵ Lam¹⁸ and Curren and Gale,⁹ may aid in conserving functioning lung tissue and minimizing the amount of skeletal deformity by reducing the extent of the thoracoplasty required to obliterate the empyema space

If tuberculous empyema persists over an uncontrolled lung, thoracoplasty may be indicated Recent work indicates, however, that it may be preferable to proceed with lobectomy or segmental resection and decortication of the remaining lung, which is then encouraged to expand rapidly to obliterate the pleural space²⁹ In early cases it may not be necessary to remove the parietal pleura

Pneumonectomy may be required if the disease is not limited

to one lobe (or to two lobes of the right lung), or the interlobar fissure may be so firmly obliterated as to preclude lobectomy. Under these circumstances, an extrapleural pneumonectomy with total pleurectomy should be performed to eradicate en bloc the pulmonary and pleural disease²⁸

Streptomycin is given during the pre- and postoperative period parenterally and is injected after pneumonectomy and pleurectomy into the "pleural" cavity with buffered phosphate solution to control the pH of the medium²⁸

Spontaneous pneumothorax and mixed-infection empyema are usually the result of damage to the lung during operation or rupture of the wall of a ballooning cavity. Hitherto the accepted treatment has been aspiration of air and fluid by needle or closed intercostal drainage tube. In a small proportion of such cases the fistula closed spontaneously and the empyema could then be treated as a tuberculous one by aspirations and lung expansion. If the empyema persisted, thoracostomy drainage, thoracoplasty and Schedé resection of the parietal pleura were usually advised. However, this complication treated in this manner has been one of the greatest causes of death following pneumonolysis.

The accepted method of treatment in the future for this condition, if the status of the other lung permits, may be immediate resection of the diseased portion of the lung with associated antibiotic therapy. Lobectomy (or segmental resection) is the more desirable operation and we know of several cases treated successfully in this manner. Extrapleural pneumonectomy and total pleurectomy²⁸ will be required if the entire lung is diseased or if no interlobar fissure can be developed to permit lobectomy in otherwise suitable cases.

Results It is usually estimated that from 40 to 50 per cent of pneumothorax failures are caused by adhesions. Matson found this to be true in 40 per cent of the 245 failures in his 1400 pneumothorax cases.

By the procedure of closed pneumonolysis, approximately 70 per cent (in our series, 71 per cent) of cases of pneumothorax unsatisfactory because of adhesions can be converted into a complete or satisfactory collapse with cavity closure and sputum conversion. It is of importance to note that the procedure carries with it practically no mortality. Also, many of the patients whose adhesions cannot be cut, and a good number of those who develop post-pneumonolysis complications, can still go on to thoracoplasty or an excisional procedure.

CONCLUSIONS

The indications, contraindications, complications and results of closed pneumonolysis have been discussed.

The technique of enucleating adhesions have been presented
A series of cases from one sanatorium, operated during a period of ten years, has been the basis for this paper

SUMMARY

Maurer's enucleation technique in closed pneumonolysis has rendered obsolete the classical Jacobeus method of dividing adhesions

The enucleation technique has increased the scope of closed pneumonolysis while reducing the incidence of pleural complications

RESUMEN Y CONCLUSIONES

La operación de enucleación de Maurer en la neumonolisis cerrada ha hecho anticuado el método clasico de Jacobeus de seccionar adherencias

La tecnica de enucleación ha extendido el campo de la neumonolisis cerrada y ha reducido la frecuencia de complicaciones pleurales

1) Se han discutido las indicaciones, contraindicaciones, complicaciones y resultados de la neumonolisis cerrada

2) Se ha presentado la técnica de enucleación de adherencias

3) Se ha basado este trabajo en una serie de casos de un sanatorio, operados durante un período de diez años

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D I S C U S S I O N

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The use of pneumonolysis has changed considerably over the past few years. We no longer feel it is necessary to resort to various and sundry methods which entail a considerable amount of intrapleural surgery. I have the feeling that a number of the individuals mentioned in this paper would have been better treated by thoracoplasty rather than by pneumonolysis. The latter procedure entails a considerable amount of work which, is not only dangerous to the patient but may also lead to a rather high number of intrapleural complications.

If we are to judge that all the cases in this series are of the type shown on the screen (which probably is not true), then I think we can say that of the five cases shown by Dr Herben at least four would have been better treated by thoracoplasty. They had large cavities which were in the apex and relatively close

to the chest wall That type of case is likely to get into trouble following pneumothorax and pneumonolysis, whether done by enucleation technic or whether the adhesions are long enough to allow relatively easy severence We have come to discount that type of case entirely so far as pneumothorax and pneumonolysis are concerned In disease of that type we have resorted to primary thoracoplasty In these cases shown today, the contralateral lung was relatively good in all except one patient Undoubtedly there were many others in the series in which that was not the case However I feel certain that in these cases thoracoplasty would have given in the main a much better result

The sputum conversion record in this group was 71 per cent The sputum conversion record in well done thoracoplasty is much higher than that In our recent series, it was between 87 and 90 per cent

When one resorts to any type of extensive procedure to free adhesions from the chest wall, one is not advancing in surgery of tuberculosis but rather going back a good many years The old records on pneumonolysis, especially Matson's work, show that he had many types of gadgets for such procedures He did many operations to strip adhesions from the chest wall, and the results in those groups when finally analyzed were far from good

In this series the record of fluid runs approximately one-third of the entire group I think the essayist was fortunate in that only a relatively small number developed tuberculous empyema In a group of pneumonolyses which we reported last year, of about 1000 cases, the percentage of fluid either transient or persistent was much lower than in the group presented We must realize that the best treatment for the patient is the simplest operation, and the one which will get the patient well with the least amount of trouble

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I have been exceedingly critical of this work, because while the end results here appear to be good, it seems that in less experienced hands much more harm could come from following such practices

If intrapleural pneumonolysis were as simple a procedure as was illustrated on the slides we have seen this morning, and if the procedure could be carried out in a way similar to the manner in which it has been presented, I think we might agree with the essayist that these adhesions may be attacked However, when you get into the pleural space and look through the thora-

coscope things do not look as simple as they did on these slides. One can never see the entire adhesion at one time, seldom can you go around the adhesion as they have demonstrated here. It is necessary as a rule to start at one side and work across the adhesion and the tissues behind the adhesion are not diagrammed as they are here. You cannot always see where the intercostal vessels are. And for that reason visibility in the thorax through the thoroscope is somewhat difficult.

The results of the operative procedure are peculiarly unsuited to statistical analysis because of the many variables.

Beginning with the clinical material, the varying stages of disease, we find many wide variations in indications for pneumothorax itself. The different methods of handling pneumothorax, frequency of treatments, degree of collapse maintained in different hands — constant variables which are reflected in the end results of the operative procedure. Opinions as to how long after operation the development of tuberculous pleural infection can be attributed to the procedure, may vary. To me the operation is still suspect if a tuberculous empyema shows up within a year. Therefore we must all the more carefully individualize each case in recommending the procedure. Preoperative classification, which I find useful, divides the patients according to the urgency for pneumonolysis to be applied by the surgeon at the operating table. The first group, those in whom the procedure is feasible but not necessarily required for effective pneumothorax. If the thoroscopic view suggests the slightest difficulty in cutting adhesions the operation should be abandoned. The second group are those for whom the operation is desirable, but not imperative. Here we encounter the ordinary risks of enucleation and proceed with the operation. The third group are those in whom we may consider the procedure necessary if any reasonable chance for the patient's recovery is to be entertained. These are patients with bilateral lesions, more extensive disease or larger cavities. One side must be brought under control in order to attack the other. This group may be classified as urgent.

The startling and unexpected development of possibilities of resection in tuberculosis has a bearing on the problem of how urgent it may be to cut adhesions. On the other hand, development of technic of decortication is on the other side of the ledger in determining the extent of the disease which may be attacked. In the unilateral case with a large cavity in the upper lobe it would be better to do a lobectomy than to take chances on large adhesions.

Two unusual complications in my series may be noteworthy, one was an air embolus due to an injury to the intercostal vein

which resulted fatally on the operating table, the second was a tuberculoma resulting in certain cerebral symptoms six weeks after operation and causing death in three months Whether this was coincidental one cannot say

Closing Remarks

Foster Herben, M D , F C C P , New York City Perhaps I was unwise in omitting comment about mortality, in the 120 operative procedures enumerated this morning we encountered no mortality The percentage of sputum conversion which we attributed to the procedure alone was 71 per cent, which compares not too unfavorably with thoracoplasty

I would not like to have the impression obtain that we utilize this procedure in preference to thoracoplasty, or that we are not aware of the value of thoracoplasty or excisional surgery We do not regard this as a "fancy" procedure Having it at our disposal, we have felt that in cases in which our best judgment indicated that we might expect success, it would be our duty to employ it It stands to reason that there are cases not included in this group in which primary thoracoplasty or excisional surgery would obviously be the procedure of choice

The chief purpose of presenting this paper to you is to illustrate what can be done without apparent detriment, and to show the results obtained in a small institution where, over about 10 years, a procedure has been employed without much change in its indications

Pulmonary Resection in Tuberculosis A Correlation of Clinical Indications and Pathology*

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The purpose of this paper is to attempt to correlate the clinical indications for pulmonary resection with the gross and microscopic pathological findings of the removed specimens. The basis of our study is a series of 34 consecutive pulmonary resections for tuberculosis performed at the Missouri State Sanatorium between April 24, 1946 and December 31, 1947.

Recent advances in the fields of anesthesia, pathologic physiology of intra-thoracic organs, and improvements in surgical skill and technics have established the operation of pulmonary resection in tuberculosis as being not only feasible but an essential addition to our present knowledge for combating this disease. In the short space of eight years since the somewhat discouraging report of Dolley and Jones¹ (1940), there has been a steady decrease in mortality and complications of pulmonary resections in tuberculosis with a corresponding increase in satisfactory results. Among the factors responsible for the improved results are (1) the universal adoption of the individual ligation technic² and pleuralization of the bronchial stump, (2) improvements in the skill and technic of the surgeons and (3) improvements in anesthesia. To these may be added the use of streptomycin pre- and post-operatively. The reports following its use in the surgery of pulmonary tuberculosis have been encouraging.^{3,4}

Most reports have been concerned primarily with the clinical indications for operation and the results of various series of cases. A presentation of the gross and microscopic examinations of the removed specimens has been absent with the exception of articles by Samson,⁵ Kinsella,⁶ Churchill and Klopstock,⁷ Lorge and Du-

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fault,⁸ and Overholt and Wilson⁹ Single case reports including pathologic findings have been presented by several authors^{10 12} Meissner,¹³ by his study of the pathology of 60 pulmonary resections performed by Overholt, has given us a picture of endobronchial tuberculosis which has aided in clarifying some aspects of the problem of this type of pathology being an indication for pulmonary resection Although our series of 34 cases is too small to permit definitive or dogmatic statements, further studies would undoubtedly lead to a uniform classification of the indications and contraindications for pulmonary resections

We have tried to correlate the roentgenographic and clinical picture with the gross and microscopic findings Bronchi were carefully dissected and many sections of both bronchi and individual lobes were made Sections were stained by Hematoxylin and Eosin and also by Verhoeff Van Gieson methods This latter stain is ideal for study of the lung as it selectively stains the blood vessels, outlines alveoli, and gives much more information than the conventional H and E stains

Of our 34 resections, 25 were pneumonectomies and 9 lobectomies

TABLE I
STATUS OF PATIENTS ON JANUARY 1, 1949

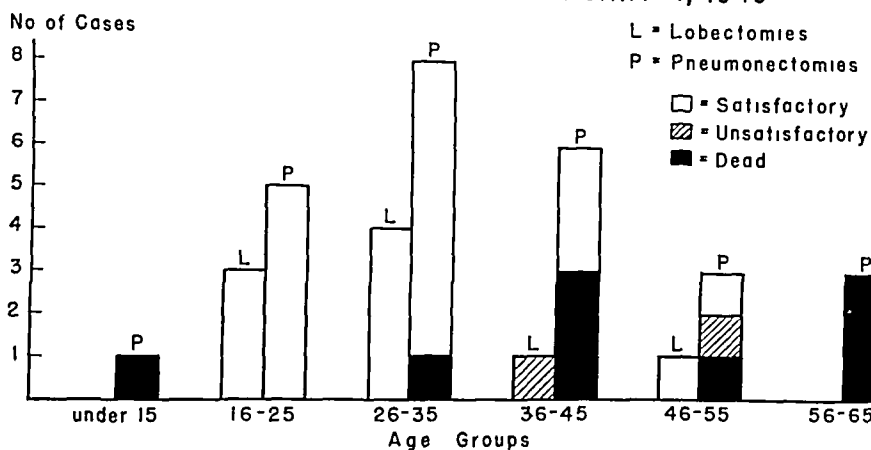


TABLE 2
Types of Operations

Left Pneumonectomy	14 cases (5 under thoracoplasty)
Left upper lobectomy	3 cases
Left lower lobectomy	2 cases (1 under thoracoplasty)
Right pneumonectomy	11 cases (4 under thoracoplasty)
Right upper lobectomy	2 cases (1 under thoracoplasty)
Right upper and middle lobectomy	1 case
Right middle and lower lobectomy	1 case (1 under thoracoplasty)
TOTAL	34 cases (12 under thoracoplasty)

A few pertinent statistics are presented in Tables 1 and 2. The youngest patient was a 10 year old colored boy who underwent pneumonectomy for a rapidly progressing caseous-pneumonic disease, the oldest was a 65 year old white female who had a residual cavity and bronchiectasis following thoracoplasty. Twelve of these cases had previous thoracoplasty on the side of the resection of whom three had contralateral pneumothoraces and one contralateral oleothorax. Another case without thoracoplasty had pneumothorax on the contralateral side.

Preoperative preparation Electrocardiograms were obtained and in some exercise tests were performed in order to evaluate the cardiac reserve. Ideally, all patients who are candidates for excisional surgery should have respiratory function tests. Vital capacity and bronchspirometric studies are misleading, often giving the surgeon a false index as to the efficiency of the remaining pulmonary tissue. In the final analysis, life depends on the diffusion of oxygen and carbon dioxide through the pulmonary alveoli. Methods of determining ventilatory function and pulmonary diffusion have been described by Ornstein¹⁴ and others, and thoracic surgeons are increasingly realizing the importance of these tests in selected cases. Although we are now contemplating the use of these tests, they were not utilized in the present series.

Contralateral pleural fixation and disease and contralateral collapse therapy obviously reduce respiratory function. Clinically we have found that contralateral pleural fixation, as the result of adhesions, re-expanded pneumothoraces and hydropneumothoraces, fibrosis from disease, and emphysema are the greatest offenders in diminishing the respiratory function.

The present series coincided with the increasing use of streptomycin pre- and postoperatively. Of the nine lobectomies, three patients received streptomycin beginning one to two weeks preoperatively for 120 days, four others received streptomycin in the late postoperative period (after three months) for occasional positive sputa. Of these, three were converted to negative. Of the 25 pneumonectomy cases, three patients received streptomycin beginning six weeks preoperatively for 120 days for extensive tracheobronchial disease involving the stem bronchus where division was anticipated. The tracheobronchial disease healed rapidly and resection was then performed without complications. Seven others were given streptomycin during the immediate pre- and postoperative period.

Four pneumonectomy cases were given streptomycin after the third postoperative month, the indications being wound infection, genito-urinary tuberculosis, late reactivation in the remaining lung, and positive sputa after resection.

Anesthesia All but two of the patients were operated under epidural anesthesia,¹⁴ the remaining two received gas anesthesia (nitrous oxide) by facial mask Postoperative bronchoscopic aspirations were not performed

Technic of operation All operations were performed with the patient in the anterolateral decubitus position The posterolateral approach was used with individual ligation of the hilar structures, interrupted suture closure of the bronchial stump, and pleuralization of the hilar structures Catheter drainage of the pleural cavity was utilized only in lobectomies in order to facilitate re-expansion of the remaining lobe or lobes Nylon suture was used throughout Between four and eight weeks postoperatively, a modified thoracoplasty was performed to obliterate the pleural space In lower lobectomies, the space was obliterated by a phrenicoclasis performed at the time of the resection

Postoperative regime Oxygen was given routinely postoperatively Water-sealed suction bottles were connected to the patients with thoracotomy tubes Except for a period of approximately 10 days before post-resection thoracoplasty, all patients were strict bed-patients for three months following resection, then they were allowed to increase their activity gradually so that by the end of the fourth month they were allowed full lavatory and dining room privileges They were placed on graduated exercises in the ninth or tenth postoperative month and were discharged as arrested cases in the twelfth or thirteenth postoperative month Thus we were able to observe these patients for at least a year following surgery

Mortality and Complications There were nine (26.5 per cent) deaths in the entire series, all occurring in pneumonectomy patients The corrected mortality rate would be 36 per cent for pneumonectomy cases and none for lobectomy cases These deaths were arbitrarily classified as "Early" or "Late", 90 days being used as the dividing line Under this classification, there were four early and five late deaths

Of the four early deaths, two occurred within 24 hours Autopsy of the first patient who had previous thoracoplasty revealed a cor pulmonale and edema of the remaining lung This patient was 65 years old, and was treated for congestive heart failure one year prior to resection (Case 11 in text) The second patient died of an unfortunate operative accident, the contralateral main bronchus having been injured during the resection, a partial stenosis resulting from the repair, and death caused by respiratory insufficiency The third patient died on the 17th postoperative day She had a contralateral oleothorax and the pneumonectomy was performed under a thoracoplasty This was also clinically a

respiratory insufficiency The fourth patient died on the 64th postoperative day, however, it occurred only two weeks following the postpneumonectomy thoracoplasty (Case 4)

Of the five late deaths occurring after the arbitrary 90 day period, the first patient died six months postoperatively This patient had a one-stage thoracoplasty with apicolysis nine years before and had a severe empyema with a broncho-pleuro-cutaneous fistula Clinically, there was evidence of amyloidosis There had been frequent attacks of hemoptysis and the resection was undertaken as a desperate life-saving resort The patient developed a gradually increasing cardio-respiratory failure which was undoubtedly the cause of death Autopsy was not obtainable The second death occurred in the seventh postoperative month This patient had previous thoracoplasty and developed symptoms and signs of cardiac failure three months after operation plus a broncho-pleural fistula and empyema in the fifth postoperative month Autopsy confirmed the clinical picture The third late death occurred in the eighth postoperative month This 62 year old male developed a wound infection, empyema and a large broncho-cutaneous fistula The fourth death was in the 10 year old colored boy who had extensive caseous-pneumonic disease for which pneumonectomy was performed Infiltration occurred in the contralateral lung in the eighth postoperative month and he died the following month (Case 12) The last death was in a 64 year old white female, who died one year postoperatively of a nontuberculous bronchopneumonia, confirmed at autopsy

Two patients developed early postoperative spread of disease Discounting the two early deaths occurring within the first 24 hours, this is an incidence of 62 per cent There was only one early postoperative spread among those having epidural anesthesia—an incidence of 33 per cent Spreading of a tuberculous process in the lungs during surgery is the result of spilling of infected sputa into previously uninvolved areas of the lungs Streptomycin materially decreases the volume of sputum and number of bacteria resulting in lowering the incidence and gravity of spreads However, we believe that epidural anesthesia is further responsible for decreasing the incidence of spreads as the patients are conscious, cooperative, and able to cough and expectorate throughout the operative procedure Both of the patients with early spreads had extensive active endobronchial tuberculosis, one of these is presented in the text (Case 3) The spread in the second patient was controlled by further thoracoplasty and she has been discharged as an arrested case

Four patients developed new infiltrations in the seventh to tenth postoperative months One with apical thoracoplasty and

contralateral pneumothorax who had upper lobectomy under the thoracoplasty developed a new infiltration in the remaining lower lobe with a positive sputum in the seventh postoperative month. The lesion is clearing under rest and streptomycin regime and sputa have been negative the past three months. The 10 year old colored boy developed contralateral disease in the eighth postoperative month and expired shortly after. Two patients developed contralateral circumscribed lesions in the tenth postoperative month with positive sputa. The lesions disappeared under rest and streptomycin, and sputa were converted to negative.

There were four cases with bronchopleural fistulae (12.5 per cent). Of these, one was temporary and not associated with empyema. Two patients had persistent fistulae with empyema developing in the second and fifth postoperative months. The fourth developed intermittent bronchopleural fistula and empyema in the 14th postoperative month. This patient was in the hospital for genito-urinary tuberculosis. The incidence of empyema was 9.4 per cent. There were three cases with wound infections (9.4 per cent). One of them had empyema and died. The other two recovered.

Present Status of Patients Of the nine lobectomy patients, five are now classified as arrested and have been discharged, two are quiescent with negative sputa, one who had previous thoracoplasty is now quiescent with an occasionally positive sputum. During the resection, the upper lobe which was the site of the major pathology could not be removed because of technical difficulties, and the source of the occasional positive sputum is thought to be from this remaining lobe. The last patient left the sanatorium in the fifth postoperative month and the status of her sputum is unknown, however, 27 months postoperatively she was radiologically negative.

Of the 16 living patients with pneumonectomies, 10 have been discharged as arrested, one is now on exercise preparatory to discharge, four are quiescent with negative sputa, and one is quiescent with positive sputum. This last case had contralateral pneumothorax which had to be re-expanded due to respiratory insufficiency. The source of the positive sputa is from this re-expanded lung. Table 3 illustrates the status of these patients at three month intervals.

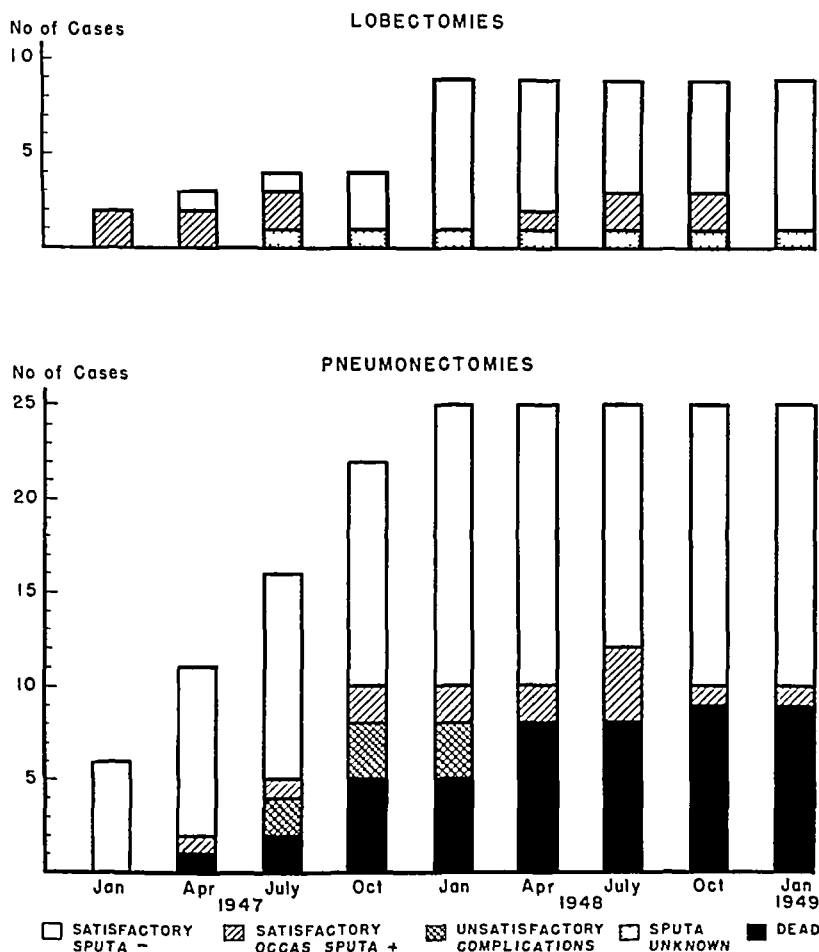
Clinical Indications for Resections

In an attempt to simplify the indications for resection in our series, we have classified the cases under five primary headings as shown in Table 4.

In addition, there were two cases thought to be nontuberculous but which on pathologic examination proved to be tuberculous,

making a total of 34 resections. We emphasize that these were the clinical indications and not the pathologic diagnoses, being based mainly on radiographic, bronchographic, and laboratory evidence. These indications are not as clear-cut as Table 4 would seem to imply. Most of these cases had several associated conditions which in themselves have been listed as proper indications by many authors. We have attempted to reduce the indications to their lowest common denominator. For example, in Group I, there were three cases with previous thoracoplasties and associated tuberculous bronchiectasis. However, as the lesions for which the thoracoplasties had been performed were radiologically apparently

TABLE III
STATUS OF CASES AT QUARTERLY INTERVALS



controlled, these cases were not classified under "Thoracoplasty Failures" In the same group, the two cases that did not have previous thoracoplasty or bronchographic evidence of bronchiectasis were pneumothorax failures One of these developed massive atelectasis of the upper lobe with continuing positive sputa and the other developed tuberculous empyema, atelectasis, and supuration of the lung Thus we find there is considerable overlapping of indications, but all of these cases had high grade bronchial stenosis which was considered the primary indication for resection

A breakdown of these primary indications is presented in outline form in Table 5 in order that the associated conditions may be better realized Many authors have listed tuberculous bronchiectasis (Group II) as an indication for resection The term has been

TABLE 4

Group I	Bronchostenosis	5 cases
Group II	Tuberculous Bronchiectasis	22 cases
Group III	Destroyed Lung with Cavitation	1 case
Group IV	Lower Lobe Cavities	2 cases
Group V	Thoracoplasty Failures	2 cases
	TOTAL	32 cases

TABLE 5

Clinical Indications for Resection

	No. of Cases
I <i>Bronchostenosis with Endobronchial Tuberculosis</i>	
A Tuberculous bronchiectasis, previous thoracoplasty	3
B Pneumothorax failure,	
1 Tuberculous empyema, atelectasis, suppuration	1
2 Atelectasis, U L	1
II <i>Tuberculous Bronchiectasis</i>	
A Without Cavitation	4
1 Atelectasis and fibrosis	3
2 Previous thoracoplasties,	
a Without empyema or B-C fistula	5
b With empyema and B-C fistula	2
3 Pneumothorax failure	1
B With Cavitation,	
1 Without atelectasis	4
2 With atelectasis and fibrosis	3
III <i>Destroyed Lung with Cavitation</i>	1
IV <i>Lower Lobe Cavity</i>	
A With tuberculous Bronchiectasis	1
B Phrenic and pneumoperitoneum failure	1
V <i>Thoracoplasty Failure</i>	
Residual cavity and bronchiectasis	2
TOTAL	32

(In 2 additional cases, resections performed for other conditions proved on pathologic examination to be tuberculous)

rather loosely applied in our series, patients having positive sputa and evidence of bronchiectasis being listed in this category. Our studies have led us to believe that this diagnosis is not easy to establish preoperatively and the condition is not as common as Table 4 would lead us to believe. A more thorough discussion of this subject will follow in the text.

All but four of these patients had positive sputa at the time of surgery. Two of the 22 tuberculous bronchiectasis patients were negative. One of them had extensive bronchiectasis and fibrosis with marked contraction of the affected lung, however, she had frequent small hemoptyses up to the time of surgery. The second patient had had negative sputa for 32 months, but during trial exercise she also had several hemoptyses. The third negative sputum patient was a 64 year old white female who was thought to have malignancy. The fourth patient was the 10 year old colored boy with extensive caseous-pneumonic disease involving the entire right lung (these last two cases make up the misdiagnosed group). His sputa were repeatedly negative and this diagnosis was not established until the pleural cavity was entered and caseous involvement of the mediastinal and hilar lymph nodes were found. There was no radiographic evidence of involvement in the contralateral lung so the decision to proceed with the resection was made at that time.

Tuberculomas and tension cavities are generally accepted indications for resection, but we had no cases of this type in our series. The preoperative diagnosis of tuberculoma is difficult to establish. Most cases of solitary circumscribed lesions are actually cavities filled with caseous material and tubercle bacilli.¹⁶ Some of these lesions excavate and refill intermittently. This type of lesion is suitable for resection as its thick walls usually withstand collapse therapy, and it is potentially dangerous as a source of tubercle bacilli. We have removed these "putty tubercles" on two occasions (one prior to and one subsequent to our series) and found rather thick cavity walls filled with caseous material and tubercle bacilli. More often, a solitary circumscribed lesion is removed with a preoperative diagnosis of "Possible Neoplasm."

The management of tension cavities has been revolutionized since the introduction of streptomycin. These cavities are always due to a valve mechanism in the draining bronchus and in most cases, endobronchial tuberculosis is the responsible factor. In our institution, tension cavities are an indication for streptomycin therapy. We have seen these cavities reduced to a fraction of their previous sizes during a course of streptomycin and in many instances, have subsequently treated them by collapse therapy. In this respect, we are not in complete accord with Maier,¹⁷ who

states that in some cases, "thoracoplasty without streptomycin is indicated. The streptomycin should be reserved for the time of resection if the latter procedure is required."

Group I — Bronchostenosis

The studies of Samson,¹⁸ Wilson,¹⁹ and others have shown that fibro-stenosis of the bronchus in a tuberculous patient is the end result of an extensive tuberculous ulcerative bronchitis. Samson⁵ was actually able to follow one case bronchoscopically from the ulcerative to the fibrostenotic stage. Apparently, the more destruction there is of the wall of a bronchus, the more extensive the resultant scar and stenosis will be. Auerbach²⁰ described these ulcerations as being lenticular, that is, their long axes are at right angles to the long axis of the bronchus. This probably contributes to the circumferential character of the stenoses.

Bronchostenosis is probably the most widely accepted indication for resection in pulmonary tuberculosis. Several surgeons, among them Baily,²¹ O'Brien,²² Alexander,²³ Brewer, Dolley and Jones,²⁴ qualify this indication by stating that only in high grade stenosis with symptoms of retention is resection preferable to thoracoplasty, primarily because of the lower mortality and morbidity associated with the latter procedure. Many of these authors prefer thoracoplasty in cases with moderate bronchostenosis without associated bronchiectasis or suppuration, even dilating the strictures between stages of thoracoplasty if indicated.

The question arises as to how often bronchial stenosis can be present without associated suppurative or bronchiectatic complications, and if none are present at the time of operation, how long will it be before they develop, even with apparently satisfactory control of the parenchymal disease. Studies have shown that various stages of endobronchial tuberculosis can be present within the same bronchus draining an active parenchymal focus, so that it is entirely possible to have various stages of active endobronchial tuberculosis distal to the stenosis. Also, once the endobronchial disease becomes established, it can and does progress independently of the parenchymal focus.¹⁹ The two most common etiologic factors in the development of bronchiectasis, namely infection and obstruction, are present in cases of endobronchial tuberculosis with stenosis.

I Bronchostenosis

A Tuberculous Bronchiectasis and Previous Thoracoplasty

There were three cases in this group. All of whom had positive sputa, previous thoracoplasties, and bronchographic evidence of bronchiectasis distal to their stenoses.

Case 1 (17668-41) VC, white female, age 25, duration of disease 5½ years Patient was first admitted June 29, 1942 with far advanced disease and positive sputum In July 1942, a left pneumothorax was instituted but abandoned, as it resulted in "ballooning" of the cavity (Fig 1a) Left phrenemphraxis was performed in December 1942, followed by three stages of posterior and one stage of anterior thoracoplasty between January and May 1943 This resulted in sputum conversion and subsequent discharge as an arrested case in October 1944 (Fig 1b, after completion of thoracoplasty) She was apparently in good health until December 1945, when she developed acute respiratory infection and positive sputa

The patient was re-admitted in June 1946 Bronchoscopy revealed extensive granulation tissue and ulceration about the left main stem bronchus (which was almost completely occluded) extending up the posterior and lateral wall of the trachea Repeated bronchoscopic treatments with 30 per cent silver nitrate resulted in only slight improvement of the endobronchial pathology Streptomycin²⁵ was administered from February 27, 1947 until June 27, 1947, a dosage of one gram daily for one week followed by 0.5 gm daily thereafter in two divided doses being employed Within four weeks after the institution of this therapy the extensive endobronchial lesion completely cleared, leaving a clean, high grade bronchial stricture just below the carina in the left main bronchus (Fig 1c, preoperative bronchogram demonstrating the stricture and the bronchiectasis) Left pneumonectomy was performed on April 15, 1947 approximately seven weeks after institution of streptomycin therapy

The pneumonectomy specimen showed numerous fibrous adhesions over the surface of the upper lobe The lymph nodes at the hilum were not remarkable On section there was a questionable thin-walled collapsed cavity at the apex Rather prominent bronchiectasis was found in the region of this cavity with evident increased fibrosis around the bronchi The microscopic sections showed little active disease The apex demonstrated secondary bronchiectasis with a few rare submucosal tubercles Rather prominent hypertrophy of the muscularis mucosa of the bronchi leading to the upper lobe was present The point of stricture in the main bronchus was not included in the resection The microscopic diagnosis was encapsulated caseous foci and bronchiectasis, predominantly non-specific, with occasional submucosal tubercles

Postoperative course was uneventful Sputa remained negative and the patient was discharged one year later as an arrested case (Fig 1d)

Comment The other two cases in this group were quite similar preoperatively, having apparently satisfactory thoracoplastic collapses without sputum conversion The second case, a 33 year old colored girl, also received streptomycin pre- and postoperatively The pathologic specimen also showed encapsulated caseous foci and predominantly non-specific bronchiectasis Although this patient had a high grade bronchial stenosis there were no symptoms of secondary suppuration or infection This type of pathologic process, however, seems to us to be an ideal indication for pneumonectomy with eradication of a non-functioning lung which remains a focus of positive sputum In the third case streptomycin was not given preoperatively Pneumonectomy was attempted, but

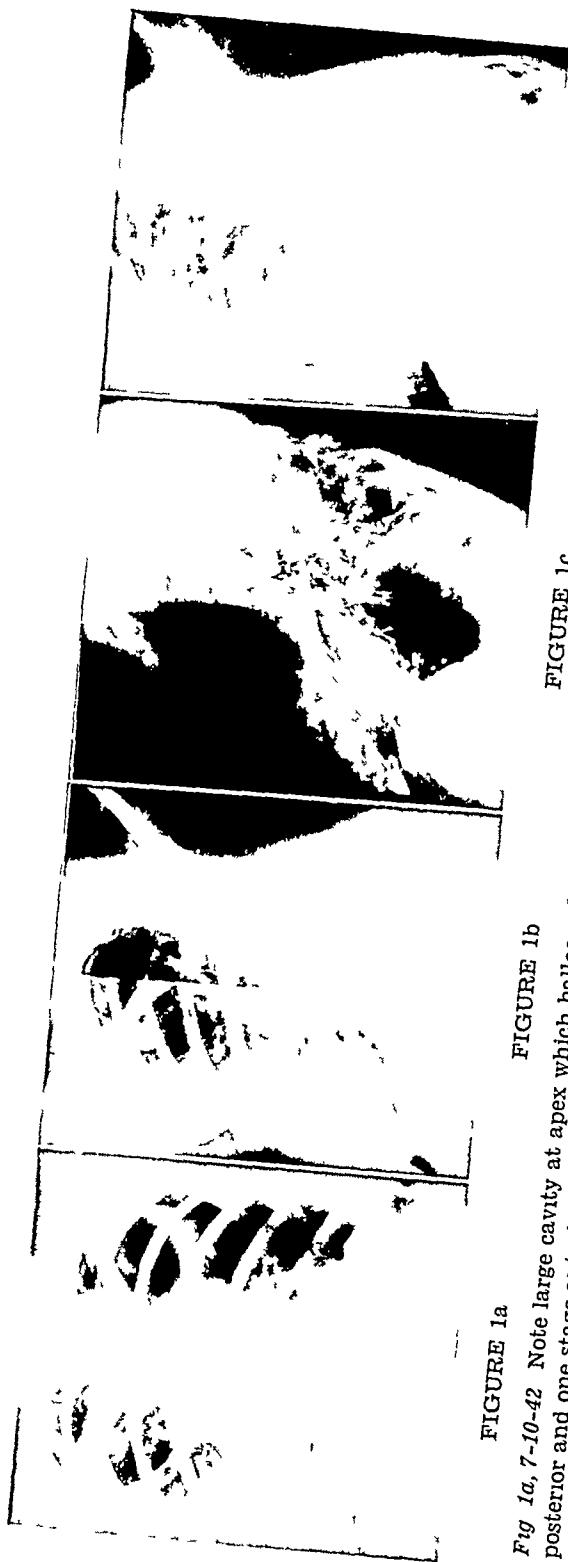


FIGURE 1a

FIGURE 1b

FIGURE 1c

FIGURE 1d

Fig 1a, 7-10-42 Note large cavity at apex which ballooned out following institution of pneumothorax — *Fig 1b, 8-11-43* Three stage posterior and one stage anterior thoracoplasty completed — *Fig 1c, 2-11-47* Lipiodol demonstrates bronchiectasis and bronchial stricture — *Fig 1d, 7-19-48* Postpneumonectomy film (15 months)

due to technical difficulties, only the lower and middle lobes were removed. This specimen contained acinous and acinous nodose foci and fibrosis in addition to the encapsulated caseous foci. Within the ectatic bronchi, there was extensive tuberculous involvement of the medium and small bronchi. The hilar lymph nodes were also involved with tuberculosis (Fig 2). We felt that the pathologic findings in this case justified the removal of these lobes. However, the major pathology in the beginning was in the upper lobe which originally was atelectatic and contained a cavity. This lobe was left behind. As the contralateral lung was radiologically negative and as the bronchial stump was healed, it is highly probable that the occasional positive sputum this patient developed one year after resection was coming from the remaining lobe or its bronchi.

In case 1, streptomycin produced a marked change in the visible endobronchial disease, and the pathologic specimen revealed practically no active disease in the parenchyma or bronchi.

Mild to moderate endobronchial disease that responds to streptomycin therapy is per se not an indication for resection, as other forms of collapse therapy may suffice in arresting the disease process. In healing severe endobronchial disease with streptomycin, varying degrees of cicatrization and stenosis will occur. Such



FIGURE 2 Pneumonectomy specimen. Note complete collapse of the lung with encapsulated caseous foci and bronchiectasis.



FIGURE 3a

FIGURE 3b

FIGURE 3c

FIGURE 3d

Fig 3a, 8-2-43 Note soft infiltration in left apex —*Fig 3b, 4-9-45* Ineffective pneumothorax with deviation of the mediastinum to the left —*Fig 3c, 11-9-45* Collapsed lung, left, with high diaphragm due to phrenicectomy —*Fig 3d, 12-1-47* Six months post-pneumonectomy

stenoses will lead to pulmonary suppuration and bronchiectasis, which in themselves are indications for resection. As in case 1 above, streptomycin is now converting cases formerly considered unsuitable for surgery into suitable risks by lowering the operative risk and decreasing operative morbidity and mortality.

B *Pneumothorax Failure*

There were two patients in this subgroup, both having high grade bronchial stenoses. Pneumothorax was instituted in both cases with varying consequences. In case 2 presented below, atelectasis and suppuration of the lung and tuberculous empyema occurred. In the second case, atelectasis of the upper lobe resulted immediately after institution of the pneumothorax.

Case 2 (16374-61) R L V White female, age 45, duration of disease five years. Onset was accompanied by laryngeal symptoms in October 1942. She entered the Missouri State Sanatorium in July 1943, but left against medical advice three months later (Fig 3a). While at home, symptoms became worse so she re-entered in April 1944. X-ray on second admission showed considerable progression of the disease in the left lung with multiple areas of rarefaction throughout.

Left pneumothorax was instituted on April 20, 1944. Closed intrapleural pneumonolysis was attempted in May 1944, but the adhesions could not be cut. The pneumothorax was re-expanded and a left phrenempharaxis was performed on June 7, 1944, resulting in a marked rise of this hemidiaphragm. The patient continued to be quite toxic with wheezing and severe cough. Bronchoscopic examination January 12, 1945 revealed extensive endobronchial disease about the left main stem bronchus which was completely obstructed with granulation tissue. The area was cauterized repeatedly with 30 per cent silver nitrate at four to six week intervals with slight improvement (Fig 3b shows status of lungs on April 9, 1945). In June 1945, she developed empyema in the left chest which proved to be tuberculous. This was treated semi-weekly by aspiration, irrigation, and instillation of Azo-chloramide with tetradecyl sulfate. The empyema cleared and became bacteriologically negative by October 1945. Left pneumonectomy was considered at this time but the active endobronchial disease in the main-stem bronchus at the level of the carina seemed to contraindicate operation (Fig 3c, taken November 9, 1945. Negative pressure was adjusted to -36 cm of water after each aspiration with no further re-expansion of this lung. Note the massive atelectasis and mediastinal shift to the left).

Streptomycin therapy was started on April 27, 1947 consisting of one gram daily for one week then 0.5 grams daily, given in two divided doses. The treatment was continued for six months. Bronchoscopy on June 13, 1947 (seven weeks after institution of streptomycin therapy) disclosed complete clearing of the granulation tissue about the carina and the left main bronchus, but marked stenosis was observed just inside the left main stem bronchus. Left pneumonectomy was performed on June 18, 1947 (Fig 3d, x-ray following left pneumonectomy and modified thoracoplasty. The scattered markings in the right lung are due to residual oil).

The pneumonectomy specimen revealed a greatly thickened pleura measuring up to 0.3 cm. The lung was firm and practically non-crepitant. A bronchial stricture which had been present was not included in the specimen. No harm apparently resulted in two cases in which strictures were left behind. On section of the lung there were large areas of caseation encapsulated by fibrous walls. These areas were extensive throughout the entire lung and the intervening pulmonary parenchyma was collapsed. These caseous areas impinged upon the bronchi and some of the smaller ones were filled with caseous material. Microscopic section demonstrated the encapsulated caseous foci with intervening collapsed lung. In addition, there was active tuberculosis within the thickened pleura. Hilar lymph nodes were negative. The microscopic diagnosis was multiple caseous foci, tuberculosis of moderate sized bronchi, caseous tuberculosis of the pleura, atelectasis and fibrosis. The sputum immediately became negative and the patient was discharged as an arrested case one year later.

Comment From these findings, it is obvious that this patient had extensive tuberculosis of the bronchi and that pneumothorax was contraindicated. There was ulceration of some of the bronchi with secondary destruction of the bronchial cartilages. As this lung was the main source of the tuberculosis, it was constantly seeding the opposite lung. The lung itself was non-functioning and tending to heal. The pathologic changes, together with the stricture, made this an ideal case for pneumonectomy.

The second case of this subgroup had extensive involvement of the left main bronchus with low grade stenosis, but in addition, had tuberculous granulations and ulcerations about the left upper lobe bronchus with moderate stenosis. Although resection of the left upper lobe was contemplated, pneumothorax was first tried cautiously, but resulted in massive atelectasis of the upper lobe. Streptomycin was not available at this time. The lobectomy specimen (left upper lobe) showed encapsulated caseous foci, bronchiectasis with extensive endobronchial tuberculosis, and tuberculosis of the hilar lymph nodes. This case presented involvement of both the bronchi and parenchyma. It is obvious that pneumothorax was contraindicated in the presence of extensive endobronchial disease and bronchostenosis.

II Tuberculous Bronchiectasis

Tuberculous bronchiectasis as a clinical indication for resection has been applied quite loosely in our series, cases presenting bronchographic evidence of bronchiectasis with a positive sputum were placed in this category. In tuberculosis, most cases of bronchiectasis follow previous parenchymal and/or bronchial disease. If tuberculosis of any extent involves the parenchyma of the lung, the bronchi leading to this involved area invariably show some degree of tuberculosis. With healing of the parenchymal process,

some degree of residual bronchiectasis remains. Usually it is asymptomatic and is in the upper lobe. If bronchograms are done, they may reveal structural alterations which will usually directly vary with the severity of the previous process. These bronchiectatic areas may show an occasional tubercle but it is questionable whether such changes should be dignified by the name tuberculous bronchiectasis. Bronchiectasis (mainly non specific, etiology tuberculosis) would seem to be a better diagnosis. In other instances (a much lower percentage) the degree of endobronchial tuberculosis may be prominent. In these cases the process can involve all sized bronchi. The pathology seen can be varied and bronchiectasis is an inevitable accompaniment. Our upper lobe bronchiectasis usually represented a burned out tuberculous process while the lower lobe bronchiectasis often showed active extensive endobronchial tuberculosis. Such changes could be designated as bronchiectasis with prominent endobronchial tuberculosis.

Rilance and Gerstl,²⁶ from their studies of 47 tuberculous patients with bronchiectasis, attempted to differentiate tuberculous and non-tuberculous bronchiectasis. But they differentiated the two conditions from a morphologic and etiologic basis. On the other hand, Mitchell and Thornton²⁷ stress the importance of positive sputum in establishing the diagnosis of tuberculous bronchiectasis.

From the surgeon's viewpoint, the diagnosis of tuberculous bronchiectasis should be made on a pathologic basis, difficult though this may be, as this condition is a surgical disease, amenable at this time only to resection. Through our studies, we feel that even though it is difficult to establish a diagnosis of tuberculous bronchiectasis, one can arrive at it in many cases with a reasonable degree of accuracy.

The endobronchial tuberculosis in an ectatic bronchus may range from an isolated tubercle (Fig 4a), ulceration into a bronchus (Fig 4b), to partial and complete destruction of the bronchial wall with obstruction and stenosis (Fig 4c shows destruction of the bronchial wall). In diagnosing bronchiectasis with endobronchial tuberculosis the question arises as to where the dividing line may be between those cases with only rare submucosal tubercles and those with extensive involvement of the bronchi. From a practical point of view we now feel justified in making this diagnosis in the presence of persistently positive sputum, bronchographic evidence of bronchiectasis with absence of active parenchymal lesions, and with bronchoscopic evidence of disease. The location of the bronchiectasis may also furnish a clue. For example, of the 22 resection cases in the tuberculous bronchiectasis group (Group II), 11 had the bronchiectasis limited to the upper lobe.



FIGURE 4a

FIGURE 4b

FIGURE 4c

Fig 4a Photomicrograph to demonstrate a submucosal tubercle. Note the overlying mucosa is intact—*Fig 4b* Ulceration of a submucosal tubercle into a bronchus. Lining bronchial epithelium is to the left—*Fig 4c* Photomicrograph which demonstrates an ectatic bronchus partially destroyed by tuberculous granulation tissue

Of these, only one had moderately extensive endobronchial disease, the remainder having predominantly non-specific bronchiectasis. On the other hand, in the 11 remaining cases that had pathology in the middle and/or lower lobes, six had moderate to extensive endobronchial tuberculosis. The old axiom "upper lobe bronchiectasis, tuberculosis, lower lobe bronchiectasis, non-tuberculosis" is founded upon an etiological classification and certainly does not hold true in our cases.

Pathogenesis The discussion of the pathogenesis of tuberculous bronchiectasis resolves into a discussion of bronchiectasis and of endobronchial tuberculosis. The presence of some degree of bronchial block plus bronchial infection is generally accepted as being a common cause of bronchiectasis. Foreign bodies, endobronchial disease, tumors, enlarged peribronchial lymph nodes, and mechanical kinking of a bronchus as seen frequently following thoracoplasty or extensive fibrotic disease may all partially occlude a bronchus with stagnation of secretions and infection distal to the point of partial block. The importance of atelectasis of the lung exerting an external pull on the bronchus as an etiological factor has been emphasized by Andrus²⁸ and Kent²⁹. Hedblom³⁰ and others have also emphasized the effect of retracting parenchymal lesions with resultant fibrosis exerting a distorting effect on the bronchi, causing bronchiectasis. It is reasonable to assume that bronchiectasis can be caused by all these various factors and that different ones may cause bronchiectasis in various areas of the same tuberculous lung.

The pathogenesis of endobronchial tuberculosis has been the subject of considerable controversy in the literature. Theories have been advanced as to the mode of implantation of the tubercle bacillus in the bronchial submucosa. The lesions are in most cases secondary to a parenchymal focus and may take root in a bronchus by

- 1) Direct implantation upon the mucosa,
- 2) Direct extension from neighboring structures, e.g. lymph nodes,
- 3) Spreading through the lymphatic system from the parenchymal focus,
- 4) Spreading through the blood stream.

Burgher, Littig and Culp³¹ and later Huang,³² from their study of 122 and 115 autopsy cases respectively, concluded that the predominant mode of infection was by direct implantation of tubercle bacilli upon the bronchial mucosa from the parenchymal focus. Silverman,³³ from a study of 110 autopsy cases, also arrived at the same conclusion.

Reichle and Frost,³⁴ from their study of 37 necropsies, concluded

that the predominant mode of infection was from the lung parenchyma through the lymphatics to the adjacent bronchi, and also that the peribronchial tuberculous lymph nodes may play a part in infection of the mucous glands of the bronchi by contiguous infection Meissner¹³ also believes that the lymphatics carry the bacteria from the parenchymal focus to the bronchial walls, this conclusion being drawn from his study of 60 surgical specimens. He found a high incidence of hilar lymph node involvement in these cases and stated, "Many of the lymphatics drain down the wall of the bronchus, the submucosa of the bronchus is also rich in lymphatics. Thus, the entire course of the bronchus which leads from a parenchymal lesion is potentially subject to tuberculosis if tubercle bacilli will but lodge in its walls."

Miller,³⁵ from his studies of the valves in the lymphatic system of the lung, concluded that the flow of lymph in the bronchial and arterial lymphatics was towards the interior of the lung that is, from the hilum toward the periphery, whereas the flow of the lymphatics accompanying the pulmonary veins and its branches is from the periphery toward the hilum. The flow of lymph at the communications of the superficial (pleural) and deep (pulmonary) set of lymphatics is always toward the pleura. Thus, it is hard to conceive of an extensive tuberculous process in the bronchi occurring consistently in a retrograde fashion from a parenchymal lesion down to the main bronchi.

Ornstein and Epstein³⁶ diagnosed tuberculous bronchitis clinically in eight cases with little or no manifest parenchymal disease. They believed that the infection was transmitted from the adjacent tuberculous lymph nodes by contiguity, and that reinfection of the parenchyma in some of these cases was caused by aspiration of the tubercle bacilli from the bronchial lesions. Silverman³³ reports one case in her series of tuberculous autopsies that had miliary dissemination without cavity formation, in which extensive tuberculosis of the walls of the small bronchi were found.

The tubercle bacillus is notorious in spreading through the path of least resistance, so undoubtedly all of the various modes of spread can and do occur as reported by the different investigators above. However, the most common method by which tuberculosis infects the bronchi appears to be by direct implantation.

In addition to the study of the surgical specimens, we have had the opportunity of following the clinical course of our patients before resection. As result of this correlated study, we feel that the mode of causation of the endobronchial pathology in our series was predominantly if not entirely by direct implantation. The incidence of endobronchial tuberculous infection in lower lobe bronchiectasis (55 per cent) of 11 cases was considerably higher



FIGURE 5 Photomicrograph which demonstrates (a above) an open duct leading to (b, below) a tuberculous lesion associated with the mucous glands

than in the upper lobe bronchiectasis (9 per cent) of 11 cases. Five of the cases in this group had previous thoracoplasties. In three with lower lobe bronchiectasis below thoracoplasties, there was rather extensive tuberculous involvement of the bronchi, whereas in the two cases of upper lobe involvement, the bronchiectasis was non-specific. Furthermore, the predominant pathology for which the thoracoplasty was performed was in the upper portion of the lung. In bronchiectasis, because of dependent drainage, cases with lower lobe pathology give rise to varying symptoms, whereas cases with upper lobe pathology are relatively symptom free. The dependency of the lower lobe bronchi in these cases might have favored more prolonged contact of the tubercle bacilli with the bronchial mucosa resulting in their implantation. In our studies, as were Meissner,¹³ Reichle and Frost,³⁴ and Silverman,³³ we were impressed by the frequency of the presence of submucosal tubercles near mucous glands and ducts (Fig 5a). Mucous ducts are quite abundant and it is reasonable to assume that the tubercle bacilli gain entrance to the submucosal tissues by this route (Fig 5b).

Group II — Tuberculous Bronchiectasis

A Without Cavitation

There were four cases in this sub-group, all with positive sputa and evidence of bronchiectasis. There was no roentgenologic evidence of atelectasis.

Case 3 (17364-1) BS White female, age 21, duration of disease at time of resection was eight months. Onset was gradual with productive cough, fever, and chest pains in August 1945. In December, she raised some blood streaked sputa, and entered the sanatorium January 1, 1946 with minimal tuberculosis of the left lower lobe and positive sputum. Bronchoscopy on January 11 revealed extensive ulcero-granulomatous lesions below the left upper lobe bronchus which were cauterized with 30 per cent silver nitrate. By March 15, the lesions had cleared (Figs 6a and 6b). Left lower lobectomy was performed on April 24, 1946. This failed to convert her sputum, and an x-ray film three months postoperatively revealed ipsilateral and contralateral infiltrations. Bronchoscopy on August 2 revealed an ulcero-granulomatous lesion about the upper lobe orifice.

The larger bronchi of the left lower lobectomy specimen showed no evidence of ulceration. In the smaller bronchi were prominent granulomatous tuberculous masses growing within their lumina, and in some instances the small bronchi were completely occluded. The lung draining these partially or completely occluded bronchi demonstrated variable degrees of atelectasis and emphysema. The microscopic findings showed striking changes in the moderate-sized and smaller bronchi. These granulomatous masses often eccentrically replaced the walls of the bronchi distorting their normal configuration, ulcerating through the mucosal surfaces and partially or completely blocking the lumina (Figs 6c and

6d) The microscopic diagnosis was Bronchiectasis with endobronchial tuberculosis (extensive, productive, and occlusive) of the major and minor bronchi, tuberculosis of the hilar lymph nodes

The patient became discouraged and left the hospital against medical advice on September 24, 1946, five months postoperatively. An out-patient roentgenogram taken in July 1948 revealed complete clearing of the lesions seen three months postoperatively.

Comment This patient had extensive tuberculosis of the moderate and small sized bronchi. It was difficult to see how this process could have healed without causing permanent destruction of the lung parenchyma. This case shows with clarity how futile it would be to think that tuberculosis of the bronchi could be cured



FIGURE 6a

FIGURE 6b

Fig 6a, 3-18-46 Note slight deviation of mediastinum to the left. No demonstrable parenchymal lesion.—Fig 6b, 5-29-46 Bronchograms revealing bronchiectasis of left lower lobe.



FIGURE 6c

FIGURE 6d

Fig 6c Photomicrograph Small bronchus is partially destroyed by tuberculous granulation tissue.—Fig 6d Photomicrograph Eccentric partial occlusion of medium sized bronchus by tuberculous granulation tissue.

with silver nitrate cauterization of the major bronchi when such extensive tuberculosis of the minor bronchi exists. It demonstrates that collapse therapy in treating such productive endobronchial lesions could not be expected to cause any appreciable improvement, and might exacerbate rather than diminish symptoms. From the findings listed above, we feel that removal of this lobe was justified.

At the other extreme, the left upper lobe was removed from a 52 year old female with tuberculosis for a period of 30 years. This patient had positive sputum demonstrable only by culture, and bilateral fibro-calcific infiltration throughout the upper portions of both lungs, with evidence of bronchiectasis in the left upper lobe. This specimen revealed a non-functioning lobe with well encapsulated caseous nodules and considerable secondary non-tuberculous bronchiectasis. It is questionable whether this lobectomy was indicated, as the presence of predominantly nonspecific and symptomless bronchiectasis in an upper lobe in a patient with few signs and symptoms is not an indication for pulmonary resection.

1 *With Atelectasis and Fibrosis*

There were three cases of tuberculous bronchiectasis without cavitation but with atelectasis and fibrosis. Two were lobectomies and one a pneumonectomy. This latter case and one of the lobectomies had negative sputa but the lungs presented the end result of extensive tuberculous processes with bronchiectasis and frequent small hemoptyses. The pneumonectomy case is presented below.

Case 4 (18005-46) A W White female, age 46, duration of disease over 13 years. She was a patient in the sanatorium from November 1934 to December 1937, at which time she was discharged as arrested. She developed a severe cold one month later and was re-admitted as a far-advanced case. She was again discharged as an arrested case in September 1939, the sputa all being negative during this period. In December 1944, she again developed positive sputum. She rested at home for a year, then returned to work. On regular check-up in October 1946, she was advised to re-enter for possible surgery, as there had been occasional small hemoptyses. She entered the Sanatorium in November 1946. She raised one to two ounces of purulent sputum in 24 hours, all specimens being negative for tubercle bacillus on smear, culture, and guinea pig inoculation. Vital capacity was 1600 cc. Electrocardiograms were within normal limits (Fig 7a is a bronchogram taken in June, 1938. Another bronchogram taken in December 1946 showed practically the same picture). Right pneumonectomy was performed on April 30, 1947.

The pneumonectomy specimen showed numerous fibrous adhesions over the surface of the lung. The hilar lymph nodes contained prominent calcification and caseation. Sections through the lung showed no evidence of cavitation but considerable bronchiectasis which was predominantly non-specific with occasional submucosal tubercles. There were

numerous calcified nodules throughout the lung and a few encapsulated caseous areas. Secondary emphysema was present (Fig 7b). The microscopic diagnosis was encapsulated caseous foci and fibrosis of the right lung, bronchiectasis, predominantly non-specific, with occasional sub-mucosal tubercles, and caseous tuberculosis of the hilar lymph nodes.

The patient had a somewhat stormy postoperative course, but felt considerably better after the fluid was aspirated and the mediastinum shifted to the right as in the preoperative film. Unfortunately, post-pneumonectomy thoracoplasty was performed on this case. When the mediastinum was again replaced to a normal position, a marked cardio-respiratory insufficiency developed and the patient expired 16 days later.

At autopsy, the contralateral lung disclosed no evidence of emphysema. There was considerable fibrosis of the pleura and lung, with edema, interstitial fibrosis, and encapsulated caseous foci. The heart was markedly enlarged (410 grams) and the walls of the hypertrophied right ventricle measured 1 cm in thickness.

Comment. This patient had considerable impairment of pulmonary reserve before operation and was up in the age group in which pneumonectomy may be dangerous. There was no evidence of bronchial obstruction. In spite of the extensive bronchiectasis the right lung had functioning pulmonary parenchyma. Death following operation was due to cardio-respiratory insufficiency. Although the contralateral lung was considerably enlarged in



FIGURE 7a



FIGURE 7b

Fig 7a Extensive bronchiectasis and atelectasis of right lung with shifting of the mediastinum to the right—Fig 7b Gross specimen with prominent mainly non-specific bronchiectasis

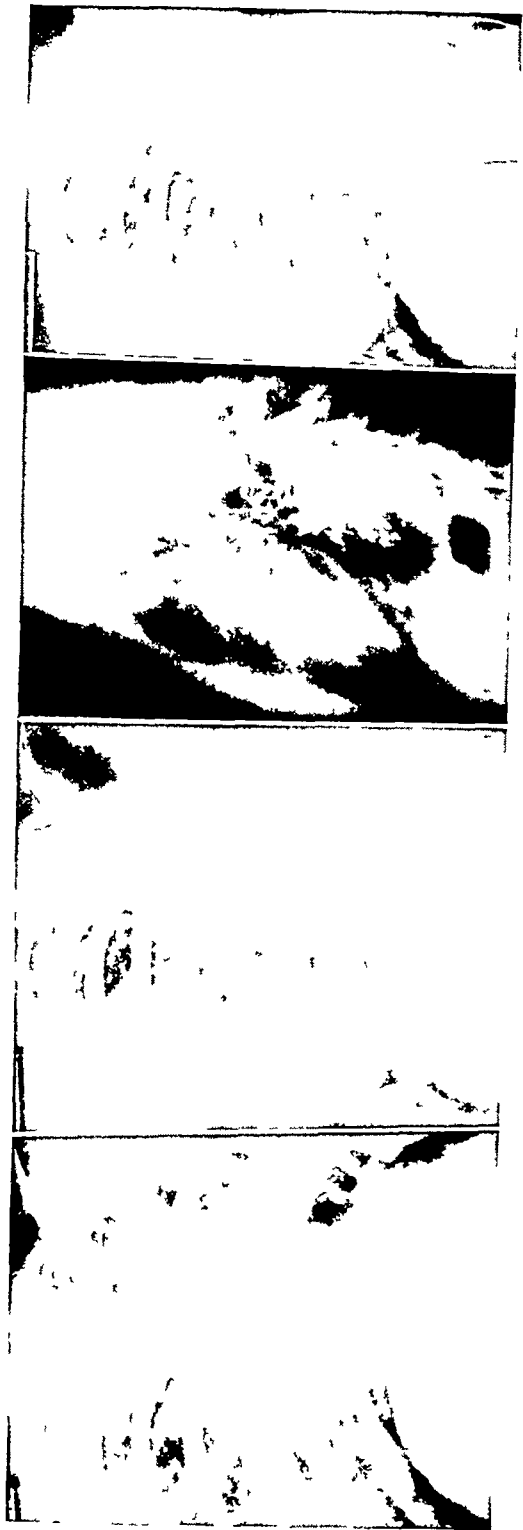


FIGURE 8a

FIGURE 8b

FIGURE 8c

FIGURE 8d

Fig 8a, 10-20-44 Note multilobular cavities with complete destruction of left lung —*Fig 8b, 5-23-46* Roentgenogram after seven rib thoracoplasty —*Fig 8c, 11-15-46* Extensive cylindrical bronchiectasis of left lower lobe —*Fig 8d, 9-2-48* Post-lobectomy film (17 months)

volume due to the marked shifting of the mediastinum to the affected side, there was no evidence of emphysema Ornstein³⁷ has stated that in cases of pulmonary resection, the contralateral lung does not become emphysematous but actually hypertrophies, and for this reason, he does not advocate post-pneumonectomy thoracoplasty to obliterate the empty pleural space Post-pneumonectomy thoracoplasties are performed primarily to prevent rapid overdilatation of the contralateral lung, thus preventing reactivation of healing or healed tuberculous lesions, and secondarily to minimize potential empyema by obliterating the pleural space However, in certain cases (as case 4 above) where there is marked shifting of the mediastinum to the involved side prior to the resection, we now feel that post-resection thoracoplasty is not necessary and may at times be harmful

Of the two lobectomy patients, one had negative sputum and was on exercise preparatory to discharge when she developed frequent hemoptyses which gradually grew in severity Changes of non-specific bronchiectasis dominated the picture in the specimen and the tuberculous infection was minimal and well controlled The second lobectomy case had positive sputum, and the bronchiectasis was borderline that is, although only rare submucosal tubercles were seen, in one section the endobronchial tuberculosis was quite prominent with granulation tissue protruding into the lumen The parenchyma showed caseous, lobular, tuberculous pneumonia which was tending to fibrose We feel that in both of these cases the resection was justified, the indications being hemoptyses in one and bronchiectasis with endobronchial tuberculosis in the other

2 Previous Thoracoplasties

a) *Without Empyema or Broncho-cutaneous Fistula* The five patients in this group had bronchographic evidence of bronchiectasis with positive sputa following thoracoplasty The lesions for which the thoracoplasties were performed were apparently controlled The bronchiectasis in all cases was present on the side of the thoracoplasty, being in the upper lobe in two and in the lower lobe in three

Case 5 (16489-36) EJS White female, age 15, duration of disease over three years Onset was acute with symptoms of a severe cold and hemoptysis in February 1944 She was admitted to the sanatorium on July 23, 1944 as a far-advanced case with severe symptoms and positive sputa She was placed on strict bed rest and left phrenemphraxis was performed in September 1944 (Fig 8a, taken after left phrenemphraxis) Pneumoperitoneums were attempted but were unsuccessful due to discomfort The left phrenemphraxis was repeated in September 1946 A seven rib thoracoplasty in two stages was performed the following February under

epidural anesthesia (Fig 8b) Sputum was not converted, and bronchoscopy revealed considerable purulent sputum in the left lower lobe bronchus Bronchograms disclosed an extensive cylindrical bronchiectasis of the left lower lobe (Fig 8c) Left lower lobectomy was performed on April 2, 1947 (Fig 8d)

The left lower lobe was practically non-crepitant The hilar region was not remarkable On section the bronchi were all moderately dilated There were numerous caseous nodules throughout the lung measuring from 0.4 to 0.7 cm Near the periphery, there were numerous small cavities which communicated with the bronchial tree Microscopically, they were seen to be dilated bronchi There were tubercles on the pleural surface and also tuberculous granulation tissue ulcerating into the walls of the small bronchi Numerous single and conglomerate caseous foci were present (Fig 8e) The microscopic diagnosis was chronic tuberculosis with encapsulated caseous foci of the left lower lobe, bronchiectasis with endobronchial tuberculosis of the medium sized bronchi, and tuberculosis of the pleura

Comment It is doubtful whether collapse therapy would have improved this situation The lobe was non-functioning and the process was tending to heal There was extensive endobronchial tuberculosis These factors seemed sufficient to justify lobectomy

The two other cases of lower lobe bronchiectasis beneath thoracoplasties were similar to the case presented above clinically, radiologically, and pathologically On the other hand, the remaining two cases who had upper lobe bronchiectasis proved pathologically to be predominantly non-specific In both of them sputum was not converted following resection, and in one, an occult cavity was demonstrated by laminagraphs in the contralateral lung In the second case, sputum was converted after further compression of the contralateral pneumothorax These two cases indicate the importance of carefully checking for presence of occult cavities and infiltrations in the opposite lung



FIGURE 8e Completely destroyed lobe with extensive bronchiectasis and encapsulated caseous foci

b) *With Empyema and Broncho-cutaneous Fistula* There were two cases in this group, both similar in that they had insufflated cavities when pneumothorax was instituted. Pneumothorax was abandoned and thoracoplasty performed, followed by tuberculous empyema and broncho-pleuro-cutaneous fistula. Both cases had bronchographic evidence of bronchiectasis with sputa and pleural drainage positive for tubercle bacilli, and showed predominantly non-specific bronchiectasis with only rare submucosal tubercles.

Case 6 (18131-77) CSR White female, age 26, duration of disease over 5½ years. Onset was gradual in March 1942. She entered another sanatorium where right pneumothorax was instituted. She entered the Missouri State Sanatorium first in August 1942 for right pneumonolysis (Fig 9a), which was followed by acute effusion. She was returned to her sanatorium in October 1942, where the pneumothorax was continued. However, because she developed empyema, bronchopleural fistula, and empyema necessitatis, she was returned to our sanatorium in January 1945 for thoracoplasty (Fig 9b). Bronchoscopy on February 10, was not remarkable except for slight narrowing of the right main bronchus. A three stage nine rib thoracoplasty was performed between February 14 and April 18. A subscapular abscess was incised and packed in June. Sputa were not converted however, and she was returned to her sanatorium six months later.

She returned for further surgery on January 26, 1947 with a broncho-pleuro-cutaneous fistula, small empyema on the side of the thoracoplasty, and a four months pregnancy. Sputum was positive for tubercle bacilli. Bronchograms revealed moderate cylindrical bronchiectasis of the right lower and middle lobes, with some puddling in a small empyema pocket (Fig 9c). A live baby was delivered normally in June 1947. Right pneumonectomy was performed on August 27, 1947. Streptomycin was administered for six weeks preoperatively and three months postoperatively, giving one gram daily for one week followed by 0.5 gram daily in two divided doses.

The right pneumonectomy specimen showed a nodular thickened pleura with a questionable bronchopleural fistula demonstrated in the upper lobe. Hilar lymph nodes showed areas of tuberculosis. On section the parenchyma was collapsed, containing numerous encapsulated caseous and calcified nodules. The bronchi were dilated with thickened walls. Microscopic examination demonstrated the fistulous tract lined by tuberculous granulation tissue. The surrounding lung parenchyma showed extensive fibrosis, encapsulated caseous foci, and collapse. There were rare tubercles in the bronchial mucosa. The microscopic diagnosis was encapsulated caseous foci, bronchopleural fistula, fibrosis, and bronchiectasis, predominantly non-specific. Following resection, the cutaneous fistula closed and the sputa became negative (Fig 9d).

Comment This patient originally had a tension cavity. The pneumothorax followed by pneumonolysis was ineffective because tuberculous empyema complicated by a broncho-pleuro-cutaneous fistula developed. The thoracoplasty slightly improved the condition but the sputum remained positive. Pneumonectomy resulted in conversion of the sputa to negative and obliteration of the

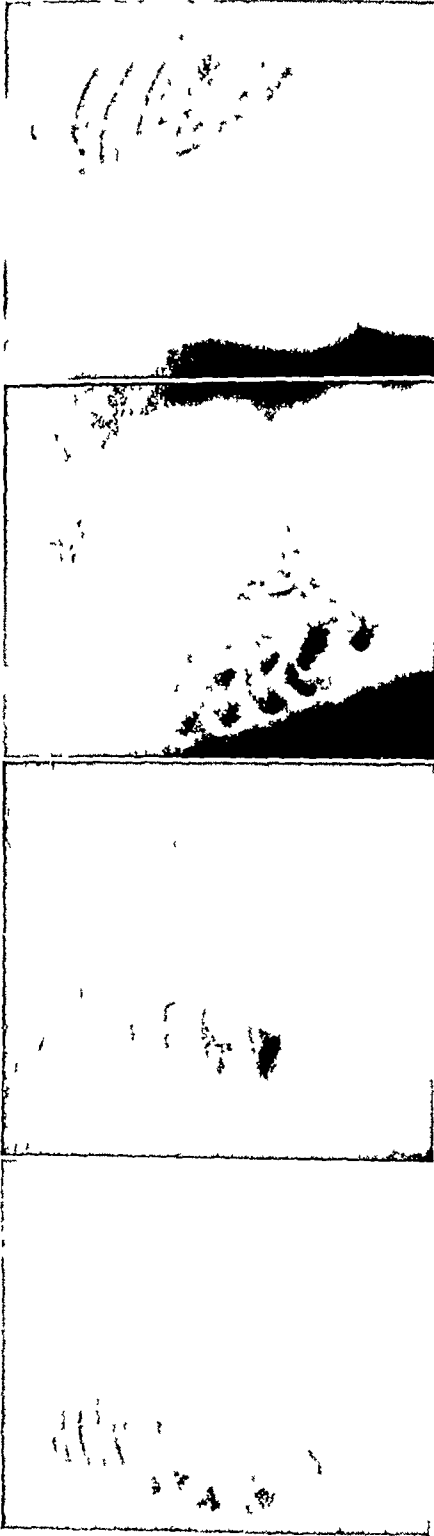


FIGURE 9a

FIGURE 9b

FIGURE 9c

FIGURE 9d

Fig 9a, 8-9-42 Right pneumothorax with persistent tension cavity —*Fig 9b, 1-30-45* Complete collapse of the right lung with bronchial pleura fistula and empyema —*Fig 9c, 2-15-47* Bronchogram with cylindrical bronchiectasis of the right lower and middle lobe with puddling in an empyema pocket —*Fig 9d, 2-27-48* X-ray taken six months post-pneumonecctomy

fistulous tract The removed lung was non-functioning Pneumonectomy was the only surgical procedure which could have brought about a cure

The second patient of this subgroup had a much larger empyema pocket with empyema of over $3\frac{1}{2}$ years' duration at the time of resection She had large hemoptyses, and resection was attempted as a life-saving procedure She had evidence of amyloid degeneration and did poorly following resection, dying six months post-operatively of cardiac failure

These two patients were classified under tuberculous bronchiectasis, as the sputa were positive and bronchiectasis was demonstrated by bronchograms Had the bronchiectasis not been demonstrated, further thoracoplasty and perhaps Schede thoracoplasty might have been considered, particularly in case 6 presented above In cases with bronchopleural and broncho-cutaneous fistula with empyema, however, we now feel that pulmonary resection is the procedure of choice and hereafter these complications will be considered as primary indications for resection Sarot and Gilbert,³⁷ Davidson and Bailey³⁸ have developed a technic of operation whereby they perform extrapleural type of pneumonectomy and attempt a total extrapleural enucleation of the empyema pocket Theoretically, this approach seems to be based on sound surgical principles Of the three cases of tuberculous and mixed empyemas in our series, the empyema pocket was entered in all and partial decortication was performed with satisfactory results in two and a late death in the third

3 *Pneumothorax Failure*

There was one patient in the series in whom pneumothorax resulted in effusion, and the collapse was insufficient to control the disease or convert the sputum Thoracoplasty was contemplated, but a routine bronchogram revealed bronchiectasis

Case 7 (17775-8) EW White male, age 25, duration of disease over three years Onset with left pleurisy in 1943 His local physician advised him to go to the Southwest, but the pains continued, so an x-ray film was finally taken in 1945 revealing an infiltration in the left upper lobe The patient entered another sanatorium in April 1945 where left pneumothorax was instituted with resultant fluid The pneumothorax was re-expanded, and the patient was referred to us in July 1946 for further treatment He had hemoptysis of approximately one pint the preceding month Bronchograms (Fig 10a) in August 1946 revealed saccular dilations of the anterior and apico-posterior segments of the left upper lobe A diagnosis of tuberculous bronchiectasis was made and left pneumonectomy was performed on October 15, 1946, followed by a modified thoracoplasty six weeks later

The left pneumonectomy specimen had a markedly thickened pleural surface The hilar region was not remarkable except for questionable

tuberculosis of the hilar lymph nodes. On section, the bronchi to the upper lobe were dilated. No cavities of the upper lobe were identified. There were numerous well defined prominent caseous nodules throughout the lung and fibrosis of the intervening lung parenchyma was pronounced. The microscopic diagnosis was encapsulated tuberculosis, and bronchiectasis with endobronchial tuberculosis. Postoperative course was smooth and the sputum was converted.

Comment This patient had unsatisfactory collapse therapy by pneumothorax. Sputum was positive and the bronchograms showed bronchiectasis. Microscopic sections further demonstrated that there was considerable tuberculosis of all bronchi and that the lung was non-functioning. There was pronounced bronchiectasis with endobronchial tuberculosis in the upper lobe and extensive acinous-nodose infiltration of the lower lobe. Figure 10b shows a section through the lower lobe.

B With Cavitation

1 Without Atelectasis

There were four cases in this subgroup, three pneumonectomies and one lobectomy. All had demonstrable cavitation, positive sputa, and bronchiectasis of the lobe in which the cavity was located. A representative case is presented.



FIGURE 10a



FIGURE 10b

Fig 10a, 8-16-46 Bronchogram demonstrates saccular dilatation of the anterior and apical posterior segments of the left upper lobe—*Fig 10b* Gross photograph of the right lower lobe which demonstrates confluent caseous lobular active tuberculous process

Case 8 (18219-94) J A White female, age 30 duration of disease seven years Onset with right pleurisy in January 1940, followed by a small hemoptysis the following month She gradually became worse and tuberculosis was diagnosed in August She first entered the sanatorium in October as a far advanced case with positive sputa A right pneumothorax was instituted in November, and although a contra-selective collapse was obtained, it resulted in sputum conversion and so was maintained until fluid developed in July 1941 The lung was gradually re-expanded by repeated aspirations and right phrenemphraxis was performed in March 1943 She was discharged as an apparently arrested case in July

Following discharge, she resumed her occupation as a beautician and was apparently in good health until August 1946, when she had an hemoptysis of three ounces She began resting at home, but in January 1947, her sputum became positive, so she was re-admitted on March 16, 1947 as a moderately advanced case At this time she had a moderate-sized cavity in the right apex, fibrosis and moderate retraction of the right upper lobe which was the site of disease 6½ years previously Bronchograms revealed saccular and cylindrical bronchiectasis involving all segments of the upper lobe (Fig 11) Right upper lobectomy was performed on October 13 1947, followed by a modified thoracoplasty with removal of the upper four ribs, the fifth having been removed at the time of the resection

The right upper lobectomy specimen showed fibrous pleural thickening at the apex There was a cavity two centimeters in its greatest diameter at the extreme apex communicating with a bronchus A confluent



FIGURE 11 4-5-47 Cylindrical and saccular bronchiectasis involving all segments of the right upper lobe

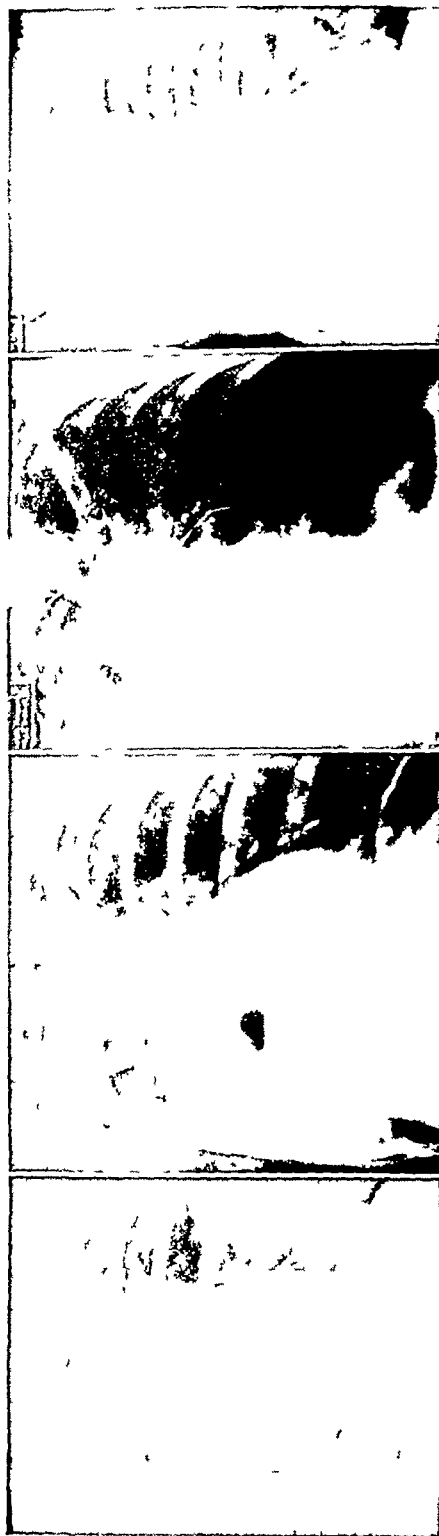


FIGURE 12a

FIGURE 12b

FIGURE 12c

FIGURE 12d

Fig 12a, 11-22-44 Extensive infiltration upper two-thirds, right lung, moderate infiltration, left mid lung field—Fig 12b, 1-17-46 Collapsed lung, right, with multiple fluid levels—Fig 12c, 1-27-47 Prominent shifting of the mediastinum to the right with pooling of oil posterior superior portion of the chest—Fig 12d, 12-1-47 Five months post-pneumonectomy

grayish-white firm tuberculous process surrounded the cavity. The sections demonstrated considerable secondary bronchiectasis in the regions of the cavity with only rare submucosal tubercles. The surrounding parenchyma showed considerable fibrous tissue and encapsulated caseous foci. The microscopic diagnosis was chronic tuberculosis with cavitation and bronchiectasis, predominantly non-specific. She has been consistently negative since surgery.

Comment This patient had a residual open chronic cavity with secondary bronchiectasis, mainly non-specific. Although the lobe was non-functioning, it is debatable whether lobectomy was indicated. The source of the positive sputum was from the open cavity. This case might have been better treated by thoracoplasty, or at least the thoracoplasty might have been tried first.

Of the remaining four cases in this subgroup, three had similar findings and resections were probably not indicated. The fourth case was a 47 year old white female who had been ill for over 17 years, had extensive bronchiectasis throughout the entire lung, and a five centimeter cavity in the apex of the lower lobe. She had a great deal of bronchial thickening, bronchiectasis, and many of these dilated bronchi revealed numerous submucosal tubercles.

2 With Atelectasis and Fibrosis

There were three cases comprising this subgroup, all having positive sputa, cavitation, atelectasis with mediastinal retraction to the affected side, and bronchographic evidence of advanced bronchiectasis. Pathologically, they were similar in that the bronchiectasis was predominantly non-specific.

Case 9 (16691-68) G.H. White female, age 39, duration of disease 5½ years. The onset was in March, 1942, with hemoptysis of one cupful, followed by cough and expectoration. However, tuberculosis was not diagnosed until a second hemoptysis in November 1944, at which time a roentgenogram was taken. She entered the sanatorium on November 21, 1944 as a far advanced case with a positive sputum and tuberculous laryngitis (Fig 12a). Treatment consisted of a right phrenemphraxis and pneumoperitoneums. Five months after the institution of this therapy she developed hydropneumothorax on the right (Fig 12b). This was treated by aspiration and re-expansion. Laryngeal lesions were treated between December 1946 and April 1947 by cauterization with 30 per cent silver nitrate, but the patient remained quite hoarse. Bronchograms demonstrated a marked deviation of the trachea to the right and extensive pooling of oil in the postero-superior portion of the chest (Fig 12c). As the contralateral lung appeared fairly stable, right pneumonectomy was performed on July 23, 1947, followed in six weeks by a modified thoracoplasty (Fig 12d). The hoarseness disappeared after correcting the tracheal deviation.

The specimen consisted of a markedly contracted right lung showing numerous adhesions and dense fibrous thickening of the pleural surface. There was moderate narrowing of the main bronchus within a few centimeters of its origin. The entire parenchyma was infiltrated with con-

fluent fibro-caseous areas. The markedly dilated bronchi contained only rare submucosal tubercles. A cavity measuring 3 x 2 x 1.4 centimeters was present in the apex, no direct bronchial communication could be established. Hilar lymph nodes contained fibrocaseous tubercles. The microscopic diagnosis was chronic tuberculosis with cavitation, encapsulated caseous foci, bronchiectasis (predominantly non-specific), and tubercles of hilar lymph nodes. The patient has had a negative sputum since the resection and was discharged as an arrested case in September 1948.

Comment. The bronchiectasis in this case and in the two others of this subgroup was predominantly non-specific, but because it was advanced and because of the extensive involvement of the parenchyma, removal of these lungs was probably justified. The bronchograms of one of the other cases of this group are presented (Figs 13a and 13b).

III Destroyed Lung with Cavitation

One case was classified in this group as we were unable to introduce iodized oil because of a markedly distorted main bronchus. Clinically, it was felt that this patient, a white female, age 21, had extensive tuberculous bronchiectasis with cavitation, atelectasis, and fibrosis. The x-ray film of the chest was quite similar to those of the three patients in the previous group. This patient had been treated for an extensive endobronchial tuberculosis which improved under silver nitrate cauterization. Streptomycin was not administered preoperatively. The pathologic sections demonstrated rather extensive endobronchial tuberculosis and bronchiectasis of the large, medium, and small bronchi, a persistent cavity, encapsulated caseous foci, atelectasis, and fibrosis. In view of the pathologic findings, we feel that this resection was justified.



FIGURE 13a

FIGURE 13b

Fig 13a and 13b Bronchograms to demonstrate extensive bronchiectasis of the right lung

IV Lower Lobe Cavity

There were two cases in this group, both with slight endobronchial involvement demonstrated bronchoscopically. In the first there was some submucosal infiltration and edema, and in the second superficial granulation tissue was present. Bronchograms on one demonstrated bronchiectasis and a primary resection was done. The second case was a phrenemphraxis and pneumoperitoneum failure, and is here presented.

Case 10 (16887-52) E A White female, age 22, duration of disease over two years. The onset was acute in the spring of 1944 with a cold, pleurisy and cough. Diagnosis was made in January 1945 and she was admitted to the sanatorium on March 13 as a far advanced case with positive sputa. There was no apparent improvement after six months of strict bed rest (Fig 14a). Right phrenemphraxis was performed in September followed by pneumoperitoneums. Bronchoscopy in October revealed some superficial granulation tissue about the left main bronchus which was cauterized with 30 per cent silver nitrate. In August 1946, there was no evidence of endobronchial disease or stenosis, however, considerable purulent sputum was seen coming from the right lower and middle lobes. Right pneumonectomy was performed on August 21, 1946, followed by a modified thoracoplasty one month later (Fig 14b).

The right pneumonectomy specimen showed hilar nodes with tuberculous involvement. On section, the upper lobe demonstrated scattered tubercles. The middle lobe was collapsed and revealed extensive bronchiectasis and endobronchial tuberculosis. In the lower lobe there was a huge cavity 7 x 5 centimeters (Fig 14c). Microscopic sections of the bronchus leading from this cavity showed ulceration of its surface and metaplasia of its epithelium, together with tubercles in its submucosa. The microscopic diagnosis was cavitation, bronchiectasis with endobronchial tuberculosis and encapsulated caseous foci of the right lower lobe, bronchiectasis and advanced endobronchial tuberculosis of the right and middle lobe bronchi, and acinous and acinous nodose foci in the right upper lobe. The sputa were converted to negative following resection. A temporary broncho-pleural fistula without empyema was present for a short time. The patient was discharged as an arrested case in December 1947.

Comment The huge cavity of the lower lobe failed to close following the phrenemphraxis and pneumoperitoneums. The changes in the middle lobe were probably secondary to the pathology in the lower lobe. From the pathologic findings it appears that pneumonectomy was indicated. The pathologic findings of the other case in this group were similar to the one presented above.

V Thoracoplasty Failure

There were two patients in this group, both having residual cavitation and bronchiectasis. They were poor operative risks and both died of cardio-respiratory failure.

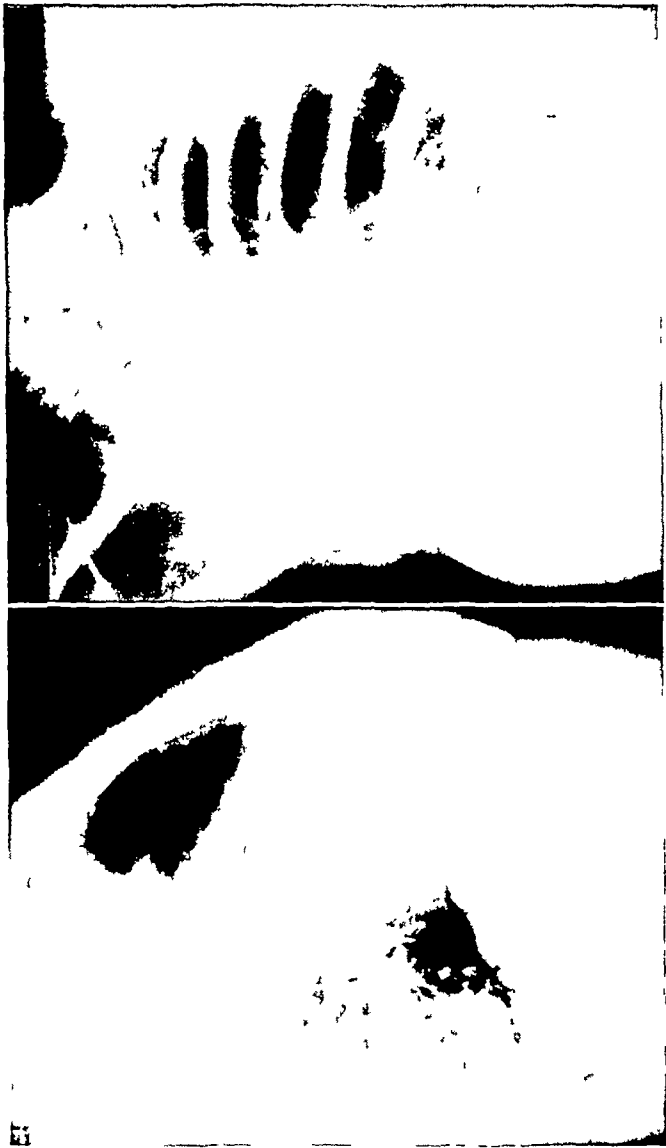


FIGURE 14a



FIGURE 14c

FIGURE 14b

Fig 14a, 8-21-45 Lateral view to demonstrate huge cavity posteriorly at the apex of the lower lobe—*Fig 14b, 5-12-47* Nine months post-pneumonectomy and thoracoplasty—*Fig 14c* Gross specimen to demonstrate huge cavity of the lower lobe

Case 11 (18374-63) BW White female, age 65, duration of disease 16½ years Onset was in January 1931 with an acute cold First admission was in July 1931 as a far advanced case with positive sputa In March 1932, right pneumothorax was attempted but was unsuccessful Right phrenemphraxis was performed the following November and the patient was discharged to another sanatorium in October 1933 as unimproved

The patient subsequently underwent three stages of right thoracoplasty at a third institution She then worked until January 1946, when she developed productive cough, dyspnea and positive sputum She was re-admitted to our sanatorium in July 1946 with a diagnosis of far advanced tuberculosis and hypertension for either a revision of the thoracoplasty or resection This was not done as she developed congestive heart failure and symptoms of toxic nephritis She was orthopneic with dependent edema and was returned to her sanatorium but insisted on resection because of severe, exhaustive cough and expectoration (Fig 15) She was re-admitted here on June 11, 1947 with a moderately enlarged and tender liver, and engorged neck veins Electrocardiograms showed left axis deviation with possible coronary insufficiency Right pneumonectomy under the thoracoplasty was performed on July 2, 1947 as a last measure The patient expired a few hours post-operatively of cardio-respiratory failure

The specimen consisted of the entire right lung in which a large cavity in the upper lobe measuring 7 centimeters in its greatest diameter was demonstrated The lung surrounding this cavity showed extensive fibrosis The middle lobe was fibrotic and the bronchi to this lobe showed peribronchial fibrosis The lumen of the bronchus to the lower lobe was narrow, and throughout this lobe were encapsulated caseous and fibrotic nodules The sections demonstrated rather prominent bronchiectasis with minimal submucosal tubercles The microscopic diagnosis was chronic tuberculosis with cavitation encapsulated caseous foci, fibrosis, and bronchiectasis with minimal endobronchial tuberculosis



FIGURE 15

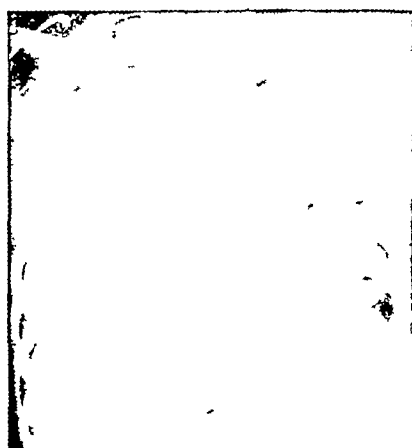


FIGURE 16

Fig 15 Residual cavity under right thoracoplasty —*Fig 16* Extensive caseous pneumonic process entire right lung

Comment Failure of collapse therapy is a generally accepted indication for resection. In cases of residual cavities following thoracoplasty, several procedures may be considered, namely, (1) revisional operation, (2) extrapleural packing, (3) some form of cavernostomy such as the flap drainage advocated by Eloesser, Rogers and Shipman,³⁹ or (4) resection. When the thoracoplasty collapse is not adequate, either the first or second procedures may be sufficient to control the disease. The flap drainage operation was performed successfully in 18 of 24 cases by Eloesser and his co-workers in dealing with insufflated cavities. However, this operation is followed by a prolonged period of convalescence. Resection is the most formidable of these procedures, but it is the most gratifying when successful.

The patient presented above was in the upper age group and died of cardio-respiratory insufficiency following operation. It appears obvious that when a patient of this age has so much damage, it is not worthwhile to undertake the risk of pneumonectomy.

The other case in this group was a 42 year old white male who also had a residual cavity and bronchiectasis. He developed symptoms and signs of cardiac failure in the third postoperative month and bronchopleural fistula with empyema in the fifth postoperative month, death occurred two months later. The surgical specimen was similar to the one previously mentioned, however, the bronchiectasis and endobronchial tuberculosis in the lower lobe was considerably more prominent than in the previous case.

Error in Diagnosis There were two cases in this series in which the preoperative diagnosis was in error. The first was a 10 year old colored boy who was thought to have non-tuberculous bronchiectasis with pulmonary suppuration. All sputum studies were negative for tubercle bacilli. Only after the chest had been opened and the caseous hilar nodes found was the correct diagnosis realized. The entire lung was of liver-like consistency. As there was no radiologic evidence of disease in the contralateral side, the decision to resect was made at that time (Fig 16). The microscopic diagnosis was caseous, lobular tuberculous pneumonia of the right lung and caseous tuberculosis of the hilar lymph nodes. This patient developed empyema of the right pleural cavity which was apparently controlled by aspirations and instillation of 50,000 units of Drisdol twice weekly. Because of his physical underdevelopment, thoracoplasty was not performed. In the eighth postoperative month, he developed a bronchopleural fistula and a spread of the disease to the contralateral lung, and died the following month.

Young patients with little resistance to tuberculosis frequently present progressive caseous-pneumonic disease. Although this pa-

tient was apparently doing well following resection until the bronchopleural fistula developed, it is doubtful whether resections are indicated in cases showing this type of pathology

The second case in this group was a 64 year old white female who was thought to have malignancy in the left upper lobe. She was the wife of a physician, and an x-ray film taken in 1942 (when she was 60 years old) was negative for any infiltration. She gave a history of frequent colds, and five weeks before admission, raised about one-half ounce of rusty sputum (Fig 17a). Sputum and bronchoscopic examinations were negative. Laminagraphs revealed what was thought to be a circumscribed mass in the upper mediastinum and upper lobe (Fig 17b). Pneumonectomy was performed, followed by thoracoplasty (Fig 17c). The surgical specimen showed a conglomerate, encapsulated caseous foci (tuberculoma-like mass) (Fig 17d). Following the resection, she had a moderate degree of

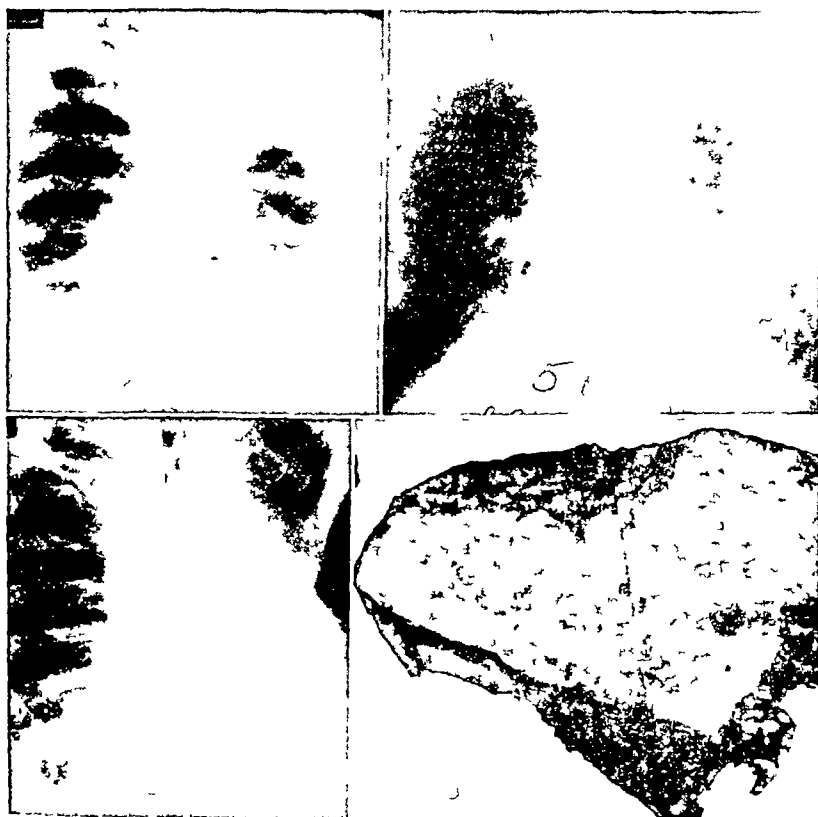


Figure 17a (above left), 7-1-46 Poorly delineated shadow left upper lobe — Figure 17b (above, right) 8-24-46 Laminagraph shows a fairly well delineated mass at left apex — Figure 17c (below, left) 3-10-47 Post-pneumonectomy film — Figure 17d (below, right) Gross specimen to show conglomerate productive tubercles simulating neoplasm roentgenologically

respiratory embarrassment, and died one year later of bronchopneumonia without evidence of reactivation of the tuberculous process (proved by autopsy) She was in the upper age group where pneumonectomy is hazardous

SUMMARY AND CONCLUSION

Thirty-four surgical specimens of tuberculous lobes and lungs were studied in order to correlate the clinical indications for resection with the pathology Although the indications for resection are not clear cut, certain statements can now be made that may aid the surgeon in the selection of suitable cases

The patient with tuberculosis has often been a chronic invalid with irreparable damage to his cardio-respiratory system The advantages to be gained from the surgical procedure should be carefully weighed against the operative risk With advancing age there is increasing morbidity and mortality, particularly from cardio-respiratory embarrassment In addition to electrocardiograms and other clinical tests for evaluating cardiac reserve, estimations of ventilatory function and oxygen and carbon dioxide diffusion in the alveoli would be ideal particularly in those cases presenting contralateral pleural fixation, collapse, fibrosis or emphysema

With the increasing availability of *streptomycin*, it should be administered preoperatively as well as postoperatively to all patients undergoing tuberculous pulmonary surgery Its use apparently decreases the incidence of spreads by reducing the total volume of sputum and the number of bacteria In certain types of cases, particularly those with *tension cavities*, the use of streptomycin may release the check-valve mechanism by healing the endobronchial tuberculosis, thus making the cavities amenable to the various collapse measures In this way, streptomycin may decrease some of the indications for resection At the same time, the drug often converts poor risk cases into cases suitable for surgery Two patients in this series with severe endobronchial tuberculosis of the stem bronchus were resected without complications after streptomycin therapy Most of our cases in whom resection was justified presented varying degrees of endobronchial tuberculosis

The incidence of early postoperative spreads was 6.2 per cent (two cases out of 32) Of the 30 patients who were operated under epidural anesthesia, there was only one spread (3.3 per cent) We feel that the use of this anesthesia was also an important factor in reducing the incidence of spreads, as the patients were conscious and co-operative, being able to cough and expectorate throughout the operative procedure

The clinical indications for resection in this series were

- 1 Bronchostenosis
- 2 Tuberculous bronchiectasis
- 3 Destroyed lung with cavitation
- 4 Lower lobe cavities
- 5 Thoracoplasty failures

Bronchostenosis, the end result of endobronchial tuberculosis, is a justifiable indication for resection. *Bronchiectasis* is almost always present distal to the stricture, usually with varying degrees of endobronchial tuberculosis. The healing of parenchymal tuberculous lesions usually results in bronchiectasis, varying in proportion to the extent of the parenchymal lesion. The resultant *upper lobe bronchiectasis* is usually non-specific and its mere presence without symptoms should not be an indication for surgery. When this pathology is present with positive sputum, careful search should be made for occult cavities or active infiltration. With upper lobe bronchiectasis plus cavitation, thoracoplasty probably should be tried first. *Bronchiectasis in the lower lung fields* is more apt to be complicated by endobronchial tuberculosis. In the absence of an active parenchymal focus but with positive sputum and evidence of bronchiectasis (condition frequently seen following adequate thoracoplasties) one may be justified in making a diagnosis of bronchiectasis with endobronchial tuberculosis. In cases presenting cavitation, massive atelectasis, fibrosis, and bronchiectasis with positive sputum (the so-called "destroyed lung") resection is the method of choice. Resection is also the procedure of choice in *chronic bronchopleural fistula with empyema*. The bronchus leading to the fistula is usually ectatic with endobronchial tuberculosis. In one of our cases, thoracoplasty alone was not successful in closing the fistula. In two, the resection was performed for hemoptyses. As the source of bleeding was from ectatic bronchi, they were classified in the "tuberculous bronchiectasis" group.

Lower lobe cavities are frequently complicated by endobronchial tuberculosis. With the introduction of streptomycin they may respond satisfactorily to collapse therapy. The two cases in this series did not receive streptomycin but the presenting pathology justified their removal. In *residual cavities following thoracoplasties*, there are several operative procedures that may be utilized, depending somewhat on the general condition and age of the patient. Resection is the most formidable of these procedures, but gives the most gratifying results. It is doubtful whether surgical resection even as a heroic measure is indicated in *caseous-pneumonic disease*. Although there were no *tuberculomas* in this series, these lesions should be resected as they often contain caseous

material and are always a potential source of spread. Radiographically, they oftentimes cannot be distinguished from neoplasms.

Future reports should state specifically the type of pathology found, particularly in those cases presenting bronchiectasis with or without endobronchial tuberculosis. Further studies may produce a uniform basis of classifying the indications and contraindications for resection in pulmonary tuberculosis, which may be further clarified by long and careful follow-up periods.

(All of the resections presented in this series were performed by Dr. W. W. Buckingham, Visiting Thoracic Surgeon. We are indebted to Dr. Charles A. Brasher, Superintendent of the Missouri State Sanatorium for his co-operation in the preparation of this paper.)

RESUMEN Y CONCLUSIONES

Con el fin de correlacionar las indicaciones clínicas para resección con la anatomía patológica, se estudiaron treinta y cuatro especímenes de lóbulos o pulmones. Aunque las indicaciones no fueron muy precisas, ahora se pueden hacer algunos asertos que pueden ayudar a los cirujanos para la selección de los casos adecuados.

El enfermo tuberculoso ha sido frecuentemente un inválido crónico con daño irreparable cardio-respiratorio. Las ventajas que pueden obtenerse de un procedimiento quirúrgico deben ser cuidadosamente estimadas frente al riesgo operatorio. Al aumentar la edad hay un aumento considerable de la morbilidad y la mortalidad, principalmente debido a los trastornos cardio-respiratorios. Además del electrocardiograma para estimar la reserva cardíaca, serían ideales las estimaciones de la ventilación y la difusión del oxígeno y de anhídrido carbónico en los alveolos, especialmente en aquellos casos que tienen fijación contralateral, colapso, fibrosis o enfisema.

Con la creciente facilidad de obtener estreptomina, se debería emplear tanto antes como después de las operaciones en todos los enfermos sujetos a cirugía pulmonar. Aparentemente su uso disminuye la frecuencia de diseminaciones al reducir el volumen, los esputos y el número de las bacterias en ellos. En algunos tipos de afección, especialmente en los que tienen cavernas hipertensivas, el uso de la estreptomina puede contrariar el mecanismo de válvula al curar la tuberculosis endobronquial y de ese modo se pueden hacer las cavernas susceptibles de responder al tratamiento por otras medidas de colapso. En cierto modo la estreptomina puede reducir las indicaciones de la resección. Al mismo tiempo la droga a menudo convierte casos que son considerados como malos riesgos, en casos adecuados para la cirugía. Dos enfermos en esta serie, con grave tuberculosis endobronquial afectando el

bronquio principal, pudieron sufrir la resección sin complicaciones después de haberse tratado con estreptomicina

La mayoría de los casos en los que la resección fue justificada presentaban grados diversos de tuberculosis endobronquial

La frecuencia de las diseminaciones postoperatorias tempranas fué de 62 por ciento (dos casos entre 32) De los 30 enfermos que fueron operados bajo anestesia epidural, solo hubo una diseminación (33 por ciento)

Creemos que el uso de esta anestesia fué también importante factor para reducir la frecuencia de las diseminaciones, pues los enfermos estaban conscientes y cooperaban, capacitados para toser y expectorar durante toda la operación

Las indicaciones clínicas para resección en estas series fueron

- 1 Broncoestenosis
- 2 Bronquiectasia tuberculosa
- 3 Destrucción pulmonar con excavación
- 4 Cavidades de lobulo inferior

Broncoestenosis, el resultado final de la tuberculosis endobronquial, es una indicación justificada de resección Siempre hay bronquiectasis distal a la estenosis generalmente con grados variados de tuberculosis endobronquial La curación de las lesiones parenquimatosas generalmente trae consecuentemente la bronquiectasis que varía en proporción a la extensión de la lesión parenquimatosa La consecuente bronquiectasia de lóbulo superior generalmente no es específica y su sola presencia sin síntomas generalmente no es una indicación para resección

Cuando este estado patológico se presenta, debe buscarse con cuidado si hay esputo positivo, para encontrar el foco activo o una excavación

En la bronquiectasis asociada a excavación en lóbulo superior la toracoplastia debe ser intentada primeramente La bronquiectasia de los campos pulmonares inferiores es mas posible que se complique con tuberculosis endobronquial En ausencia de foco activo parenquimatoso pero con esputo positivo y evidencia de bronquiectasia (cosa frecuentemente vista después de toracoplastias adecuadas) uno puede estar justificado para hacer el diagnóstico de bronquiectasia con tuberculosis endobronquial En los casos que presentan excavación, atelectasia masiva, fibrosis y bronquiectasis con esputo positivo, (el llamado "Pulmón destruido"), la resección es el procedimiento de elección

La resección es también el método de elección en la fístula broncopleurale con empiema El bronquio que conduce a la fístula es habitualmente ectásico con tuberculosis endobronquial En uno de nuestros casos la toracoplastia sola no logró clausurar la fístula En dos, la resección se realizó por hemoptisis Como la fuente de

la hemorragia fueron los bronquios ectásicos, se clasificaron como "bronquiectasia tuberculosa"

Las cavidades de lóbulo inferior frecuentemente están complicadas o con tuberculosis endobronquial. Con la introducción de la estreptomycin pueden responder satisfactoriamente al colapso. Los dos casos en estas series no usaron estreptomycin, pero la patología encontrada justificaba la extirpación. En las cavidades residuales después de toracoplastia, varios procedimientos pueden usarse dependiendo de las condiciones generales del sujeto y de su edad. La resección es el procedimiento mas formidable pero da los mas satisfactorios resultados.

Es dudoso que la resección esté indicada aun como medida heroica en la afección caseoneumónica.

Aunque en nuestra serie no hay tuberculomas, estas lesiones deben sujetarse a resección puesto que a menudo contienen material caseoso que siempre es una fuente potencial de diseminación. Radiológicamente no pueden frecuentemente distinguirse de las neoplasias.

Informaciones en el futuro podran especificar el tipo de patología encontrado particularmente en aquellos casos que presentaron bronquiectasis con o sin tuberculosis endobronquial. Estudios ulteriores podran proporcionar una base uniforme para la clasificación de las indicaciones y contraindicaciones para la resección en la tuberculosis pulmonar, lo que se aclarará mucho mas por el estudio de los enfermos seguidos largo tiempo.

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Results of Oral BCG Vaccination on 348 Families*

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At the time the planning of the present campaign against tuberculosis was initiated, the Director of the S N T did his best to include among the various investigations destined to collect the most accurate possible data, a series on the results of the B C G vaccination in our midst

With this in view, Professor Paula Souza communicated with Professor Arlindo de Assis, Director of the Vaccination Services of the Ataulpho de Paiva Foundation, who immediately placed all the data contained in his files at the disposal of the controlling organization of the antituberculosis campaign In a joint meeting, Drs Assis, Paula Souza and Lincoln de Freitas Filho invited me as a technician in biostatistics After discussing the best way in which to develop a work which would be as close as possible to natural conditions, we decided to make an investigation in families in which there were vaccinated and nonvaccinated children This would be the surest manner to guarantee social-economic, hygienic, nutritional, contagious and even hereditary conditions as similar as possible among the vaccinated and nonvaccinated children They then contemplated the preparation of a map with a series of items, as follows

1) Identification, with the following queries number of card, color, sex, date of birth, and age at the end of observation

2) Preliminary examinations x-ray film, skin tests and home environment

3) Immunization Date of the first vaccination, date of first and second revaccination, and time elapsed between the first and second vaccination, also, time elapsed between the second and third vaccination

4) Diagnosis of tuberculosis Date of diagnosis, time elapsed between the beginning of observation and the date of diagnosis,

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results from sputum test or stomach washing, results of x-ray examinations, clinical type and the evolution of the process

5) Death date of death, time elapsed between the beginning of observation and the date of death, primary cause of death, secondary cause of death and results of necropsy

6) Contagion if intra- or extra-domiciliar, degree of contagion, duration, results of the sputum examination of the contagious source, results of the radiological examination, and finally the evolution of the disease

Once the maps were prepared the Director of the SNT entrusted me with the collection of data, using the files of the BCG Service of the Ataulpho de Paiva Foundation, placed entirely at my disposal by its Director. After studying the contents of these files, I decided to include in the above mentioned maps all the families which had both vaccinated and nonvaccinated children, without bothering to separate those whose disparity in the data might make it impossible to compare the vaccinated with the nonvaccinated. This systematic inclusion facilitated a later examination, permitting a complete and immediate view of all the families included in these maps. Once this first phase was completed, I observed many uncertainties regarding the nature of the pathological findings. In order to verify the true etiology in the greatest possible number of cases, it was necessary to prepare a more detailed revision of all the suspect cases. I then divided the cases found, in two groups

1) Known tuberculous morbidity. All children presenting a pathological pulmonary x-ray picture with a positive gastric lavage, all children who had not had a gastric lavage but whose radiological findings showed a ganglio-pulmonary process of typically tuberculous appearance, and finally those x-ray shadows which, by position or other characteristics in addition to a strong positive tuberculin reaction, left no doubt that we were dealing with a case of tuberculous origin.

2) Suspected morbidity. All children whose radiograph showed an atypical pulmonary or pleuropulmonary shadow, without lymph node involvement and of unknown or slow evolution, who had not had a gastric lavage or whose lavage was negative and with negative or moderately positive skin test.

All children who had fleeting pulmonary findings (less than a month) and whose reactions to the therapeutic agents used (sulfa drugs and penicillin) were of a nonspecific nature were included among the normal children.

After I had included in the maps all the children belonging to families with vaccinated and nonvaccinated children, I could readily eliminate those whose control conditions did not allow a

comparative study So that no preconceived ideas should interfere, I made a new map from which the data of morbidity and mortality were eliminated, allowing only a revision of conditions of control and contagion Therefore, several families were eliminated with children whose age could not be correctly ascertained, or who had come to the Service for the last time at an age of less than 6 months, or even when the difference in age between the vaccinated and nonvaccinated was more than 10 years

In this manner, the number of families was reduced to 348, with 479 vaccinated, and 461 nonvaccinated children, making a total of 940 children

Studying Tables 1, 2 and 3, we discovered a great difference in the conditions of observation of the vaccinated and the control group especially with respect to the age at the beginning of observation This is easily explained by the fact that vaccination in our community is mostly directed toward newborn infants, who are placed under medical control at 3 months of age, while the

TABLE 1
Age at the Beginning of Observation

	Vaccinated		Non-vaccinated		TOTAL
	No	Per cent	No	Per cent	
Under 6 months	227	47.4	8	1.7	235
From 6 to 12 months	77	16.1	18	3.9	95
From 1 to 2 years	38	7.9	24	5.2	62
From 2 to 5 years	61	12.7	112	24.3	173
From 5 to 10 years	63	13.1	198	42.9	261
Over 10 years	13	2.7	101	21.9	114
TOTAL	479	99.9	461	99.9	940

TABLE 2
Duration of Observation

	Vaccinated		Non-vaccinated		TOTAL
	No	Per cent	No	Per cent	
Less than 3 months	55	11.5	207	44.9	262
From 3 to 6 months	23	4.9	30	6.5	53
From 6 to 12 months	60	12.5	43	9.3	103
From 1 to 2 years	112	23.3	83	18.0	195
From 2 to 5 years	153	31.9	70	15.2	223
From 5 to 10 years	76	15.8	28	6.0	104
TOTAL	479	99.9	461	99.9	940

control group includes mainly the older brothers and sisters. The latter, who have not been vaccinated at birth, seek out the Service for the tuberculin tests and in this way the possible need for vaccination is discovered.

Passing on to the study of these control data, we will examine Table 1, with reference to the age of the children at the beginning of the observation. The difference in the numbers of the vaccinated and nonvaccinated is especially significant in the age group of 0 to 6 months, which is 47.4 per cent of the vaccinated group and 1.7 per cent of the control group. Even by grouping together all the nonvaccinated children of 0 to 2 years of age the percentage hardly reaches 10 per cent of the total, while the vaccinated group who began their observation in this period, is over 70 per cent. As we know that both tuberculous morbidity and mortality in infancy, is most acute in the first two years of life, it is easy to understand that this difference in age at the beginning of observation, is a considerable disadvantage for the vaccinated group. It is a fact, therefore, that some of the nonvaccinated children of the 348 families included in this investigation, had during this period a tuberculous process of mild evolution, retrogressing completely before they came under the observation of the Service, and also, others which progressed to death and which were not computed here, because they never came for observation.

Table 2 refers to the duration of the observation period. Here also, we will find a noticeable difference between both groups, which difference also favours the control group. While the majority of vaccinated children came several times for examination to the Vaccination Service, the nonvaccinated children were examined only once in about 45 per cent of the cases. Therefore, it is clear that the group having a periodic control will reveal a higher percentage of morbidity than the group whose period of control was much shorter. (See Table 2)

Still with regard to the method by which they were controlled, Table 3, shows us the age of the children at the end of observation. Here there is a greater similarity between the two groups, it being noted that there is a greater incidence of the nonvaccinated, among those that finished the period of observation beyond 10 years of age. This fact might give us an impression of disadvantage for the nonvaccinated group if it went on until 20 years of age, in which group is found the highest incidence of tuberculosis. For this reason, we systematically cut out all cases of morbidity which occurred after the 15th year of life of the children. (See Table 3)

After having dealt with the control conditions, the next consideration is with regard to sex, race, environment and conditions

of contagion With regard to sex there is only a slight predominance of male children in the vaccinated group (See Table 4) The study of race and environment, in both groups, brings us interesting information, showing the advantage of the investigation in families Nobody ignores the importance of race and environment in the incidence of tuberculosis It is therefore, essential, that when comparing groups of vaccinated and nonvaccinated, these factors be as similar as possible The study of Tables 5 and 6 shows the distribution of race and environment in vaccinated and nonvaccinated children, which distribution can only be homogeneous through the study of families (See Tables 5 and 6)

Studying the conditions of contagion to which the children were exposed, I tried from the beginning to discriminate as much as possible between the nature and various degrees of exposure Unfortunately, I realized the difficulty in this procedure, because of the type of investigation in which the informing element is only the information card, the data of which usually are not sufficient Therefore, I divided the contagion in three groups Known, suspected and unknown I considered the contagion as *known*, when it was possible to verify the existence of intra- or extra-domiciliar contagion, with a tuberculous person discharging bacilli, or, if not knowing the sputum result, the radiographic examination, or evolution of the disease, demonstrated that the person

TABLE 3
Age at the End of Observation

	Vaccinated		Non-vaccinated		TOTAL
	No	Per cent	No	Per cent	
From 6 to 12 months	39	8.1	11	2.4	50
From 1 to 2 years	88	18.4	16	3.5	104
From 2 to 5 years	171	35.7	96	20.8	267
From 5 to 10 years	140	29.2	192	41.6	332
Over 10 years	41	8.5	146	31.6	187
TOTAL	479	99.9	461	99.9	940

TABLE 4
Sex Distribution

	Vaccinated		Non-vaccinated		TOTAL
	No	Per cent	No	Per cent	
Male	256	53.4	204	44.2	460
Female	223	46.5	257	55.7	480
TOTAL	479	99.9	461	99.9	940

was discharging bacilli *Suspected contagion* is a category for the child who lives or has lived in contact with a tuberculous person apparently cured, or also, when, in the case of collective living, there exists a tuberculous person discharging bacilli without apparent contact with the vaccinated child. Finally, I considered the contagion *unknown* when it was impossible to verify the existence of contagion, either intra- or extra-domiciliar. Without doubt, the ideal would be a classification according to the degree of exposure to contagion, as had been originally planned, but due to the impossibility of so doing, it is essential that there be a uniform criterion for the vaccinated and control groups. By ascertaining the incidence of contagion in both groups, we found that it was greater in the control group than in the vaccinated group. Adding up both types of contagion, *known* and *suspected*, this difference was slight (68.98 per cent against 63.04 per cent), but

TABLE 5
Race Distribution

	Vaccinated		Non vaccinated		TOTAL
	No	Per cent	No	Per cent	
White	290	60.5	278	60.3	568
Negro	94	19.6	103	22.3	197
Mulato	95	19.8	80	17.3	175
TOTAL	479	99.9	461	99.9	940

TABLE 6
Type of Habitation

	Vaccinated		Non-vaccinated		TOTAL
	No	Per cent	No	Per cent	
Individual	400	83.5	381	82.6	781
Collective	64	13.3	63	13.6	127
Unknown	15	3.1	17	3.7	32
TOTAL	479	99.9	461	99.9	940

TABLE 7
Incidence of Contagion

	Vaccinated		Non vaccinated		TOTAL
	No	Per cent	No	Per cent	
Known	238	49.68	286	62.04	524
Suspected	64	13.36	32	6.94	96
Unknown	177	36.95	143	31.01	320
TOTAL	479	99.99	461	99.99	940

considering only those whose contagion could be verified, the difference increases noticeably (62.04 per cent against 49.68 per cent). This is, no doubt, a factor which might influence a greater incidence of tuberculous morbidity and mortality in the control group (See Table 7). To counterbalance this apparent advantage of the vaccinated group, when we examine the age of the children at the beginning of contagion, we find that 58.6 per cent of the vaccinated group began contagion during their first year of life, while in the control group this percentage is only 22.2 per cent (See Table 8). It is unnecessary to point out the importance of the child's age when submitted to contagion as it is a generally known fact. Another important factor, beyond the time of beginning of contagion, is without doubt, its duration. In this investigation, this was very similar in both the vaccinated and nonvaccinated groups, which fact can be verified by Table 9.

Analyzing these facts, we are obliged to admit that from the statistical point of view, this work contains some faults which are impossible to correct. It is true that some comparative data among the vaccinated and control groups are profoundly diver-

TABLE 8
Age at the Beginning of Contagion

	Vaccinated		Non-vaccinated		TOTAL
	No	Per cent	No	Per cent	
First year	177	58.6	71	22.2	248
From 1 to 2 years	31	10.2	28	8.7	59
From 2 to 5 years	58	19.2	94	29.4	152
From 5 to 10 years	27	8.9	83	26.0	110
Over 10 years	9	2.9	43	13.5	52
TOTAL	302	99.8	319	99.8	621

TABLE 9
Duration of Contagion

	Vaccinated		Non-vaccinated		TOTAL
	No	Per cent	No	Per cent	
Less than 3 months	22	8.8	16	5.6	38
From 3 to 12 months	89	35.7	88	30.8	177
From 1 to 2 years	55	22.1	69	24.1	124
From 2 to 5 years	58	23.3	78	27.2	136
Over 5 years	25	10.0	35	12.2	60
TOTAL	249	99.9	286	99.8	535

gent, while others, such as race, environment, and time of exposure to contagion, are very close. What seems to us, however, of supreme importance, is the fact that, with the only exception of incidence of contagion all the divergent data favors the control group.

The criterion adopted by me for the calculation of incidence of specific morbidity in the two groups, has already been explained when I mentioned the classification of the cases found, in known and in suspected morbidity. At the same time, I removed all the findings which were proved nonspecific. Table 10 shows us the incidence of known and of suspected morbidity in the vaccinated and nonvaccinated groups, indicating that in the first case the morbidity of the control group was 4.2 times greater than that of the vaccinated group (See Table 10). We can also verify the influence of contagion in the group of known morbidity. This verification once again shows the great importance of intense contagion in early infancy, and especially in the first two years of life. Therefore, our attention is drawn to the fact that both among the vaccinated and the nonvaccinated groups, the incidence of disease cases showed a percentage of more than 80 per cent in the group of known contagion while in the group of unknown contagion the incidence of morbidity was equal to zero among the vaccinated and of 12.9 per cent among the nonvaccinated (See Table 11).

The data regarding mortality is unfortunately, very precarious. As in all ambulatory services, the knowledge of deaths is almost

TABLE 10
Tuberculous Morbidity

	Vaccinated		Non-vaccinated		TOTAL
	No	Per cent	No	Per cent	
Known cases	15	3.13	62	13.44	77
Suspected cases	5	1.04	15	3.25	20
TOTAL	20	4.17	77	16.69	97

TABLE 11
The Relation Between Known Cases and Tuberculous Contagion

	Vaccinated		Non-vaccinated		TOTAL
	No	Per cent	No	Per cent	
Known contagion	13	86.6	50	80.6	63
Suspected contagion	2	13.3	4	6.4	6
Unknown contagion	0	0	8	12.9	8
TOTAL	15	99.9	62	99.9	77

always obtained only by means of information given by relatives of the children Necropsy was done only in one case which had been hospitalized in the tuberculosis ward of the Instituto Fernandes Figueira As a consequence of these facts, probably more deaths occurred which will always be unknown, because the Vaccination Service was not notified, and also certain known cases in which death occurred sometime after the last control, leave some doubt as to the real cause of death It is however, interesting to verify the results of the findings in the Mortality File of the Service, which reveals a specific mortality of 0.41 per cent (2 cases) in the vaccinated and of 1.73 per cent (8 cases) in the nonvaccinated, or in other words, in the same manner as regards to morbidity, the specific mortality rate of the nonvaccinated group was 4.2 times greater than that of the vaccinated group

CONCLUSIONS

1) For the comparative study between vaccinated and nonvaccinated children, the investigation by families favors, without any doubt, a collection of more precise data than that carried out from heterogeneous sources

2) Even so, certain items are profoundly divergent, and in both groups, with the sole exception of the greater incidence of known contagion in the nonvaccinated group, all the other factors were of a nature to cause a greater severity in the judgement of the results of the vaccinated cases as contrasted with the nonvaccinated cases

3) The tuberculosis morbidity was of 3.13 per cent for the vaccinated group and 13.44 per cent for the control group, or, in other words, 4.2 times greater in the control group The test X^2 with the Yates correction for the verification of the significance was equal to 31.6

4) The specific mortality, like the morbidity, was also 4.2 times greater in the control group In view of the small numbers found here, the X^2 test showed here the non-existence of significance

CONCLUSOES

1) Para o estudo comparativo entre criancas vacinadas e nao vacinadas, a investigacao familiar favorece sem duvida uma coleta de dados mais precisos do que a realizada em fontes heterogeneas

2) Mesmo assim, certos itens divergem profundamente nos dois grupos, sendo que com a unica excecao da maior incidencia de contágio conhecido no grupo dos nao vacinados, todos os outros itens foram de molde a influir no sentido de um maior rigor no julgamento dos resultados da calmetizacao

3) A morbidade tuberculosa foi de 3.13% para o grupo vacinado e de 13.44% para o grupo controle, ou seja, 4.2 vezes maior no grupo controle. A prova χ^2 com a correção de Yates para a verificação de índice de significância foi igual a 31.6.

4) A mortalidade específica a exemplo da morbidade, foi também de 4.2 vezes maior no grupo controle. Em virtude dos números pequenos aqui constatados, a prova de χ^2 mostrou aqui a inexistência de significância.

The Significance of Positive Cultures*

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There have been many reports in the literature about the value and necessity of examining cultures of fasting gastric contents and sputum in persons with sputum and gastric concentrates negative for tubercle bacilli. It is a common practice for gastric cultures to be done in patients without expectoration, or with negative or unsatisfactory sputum. About 30 per cent of sputum and gastric cultures are positive and without these laboratory methods, many patients actually positive would be considered negative. There is, however, a considerable difference of opinion about the interpretation of positive cultures. There have been few reports concerning the significance of positive cultures in relation to appraisal of the arrest of the disease, prognosis, need for hospitalization, or treatment.

Ordway, Medlar and Sasano¹ raised many interesting problems about the value of cultures. They believe that only a minor percentage of patients discharged from tuberculosis institutions would fail to intermittently shed tubercle bacilli. This is also true after pneumothorax or thoracoplasty. In other words, patients may be well clinically, and not active, but pathological cure is rare. But they state it would be an unjustifiable hardship upon the tuberculous individual to segregate him indefinitely, or keep him in a sanatorium until negative by all laboratory methods.

Chang² has reported the prognostic significance of occasionally positive sputum after adequate treatment of tuberculosis. He followed for two years or more 864 patients discharged as arrested or apparently arrested. During the last six months of sanatorium care, at least six cultures were done, and if one or two were positive, the patient was considered to have an occasionally positive sputum. The reactivations of patients with sputum negative for tubercle bacilli on culture and guinea pig inoculation were compared with patients with occasionally positive sputum, and those with sputum negative on direct examination only who had no cultures. The last two groups had a comparable recurrence rate of tuberculosis which was twice that of the first group. Chang concludes that patients discharged with occasionally positive spu-

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tum experience a reactivation of their tuberculosis more frequently than those with unequivocally negative sputum

Abeles³ also studied the significance of positive cultures in apparently adequately treated pulmonary tuberculosis. One hundred ninety-nine patients discharged as apparently arrested or arrested were observed for an average period of 44 months. One hundred four patients had only negative cultures and 95 had occasional positive cultures during a six month period prior to discharge. Thirty-six of the 199 patients were readmitted to a sanatorium or treated at home for a reactivation of their disease. Twenty-five of the readmitted patients had positive cultures and 11 had negative cultures during the six months before discharge. The cumulative rate of readmissions at the end of four years following discharge was 28.5 per cent for the patients discharged with positive cultures and 10.5 per cent for those discharged with negative cultures.

Material for Study

In order to determine the significance of positive cultures, patients were selected in whom all sputum and gastric concentrates were negative and only the cultures were positive. The patients were divided in 3 groups—those with a single, occasional, or majority of the cultures positive, respectively. These positive cultures were correlated with the roentgenologic changes, clinical course, laboratory findings, treatment in the sanatorium, and the status of the patient after discharge.

Observations

Group I—Patients with a single positive culture. Group I consists of 29 patients (14 male, 15 female, with moderately advanced lesions in 14, minimal in 15, and the infiltration unilateral in 21 and bilateral in eight). These patients had but a single positive culture during their stay in the sanatorium. All other sputum and gastric concentrates and cultures were negative. No patient was included unless there was at least six months of institutional treatment after the positive culture. The average sanatorium length of stay was 8.4 months.

There were 29 positive cultures (26 gastrics, three sputum) and 191 negative cultures (174 gastric, 17 sputum), an average of one positive and 6.6 negative cultures per case. The concentrates totaled 539 (336 sputum, 203 gastric), an average of 18.5 per patient. The cases have been analyzed according to the type of infiltration and the roentgenologic changes at the time of the positive culture. This is shown in Table 1.

The terms used in describing the type of infiltration and roent-

genologic changes are defined as follows Exudative-productive—mixed infiltration with a combination of soft, hazy, ill-defined shadows and hard, nodular and linear, well demarcated lesions with the principal roentgenologic character of a soft nature in these patients, predominantly productive (exudative-productive)—mixed infiltration with some exudative elements but the total extent of the lesion mostly productive in type, productive-fibrotic—typical, hard nodular and linear infiltration Progression refers to an actual increase in the extent of lesion or cavitation Resolution means resorption of exudative areas or increase in fibrosis

The single positive culture was unassociated with any roentgenologic change in 22 patients (76 per cent of the total group), in 6 patients (20 per cent), those with a considerable or slight exudative character in the infiltration, resolution or increase of fibrosis took place, while in no patients did progression occur The resolution was usually slight in degree and appeared at various intervals after admission One positive culture was correlated with alteration in the degree of pneumothorax collapse The positive culture was of questionable significance in the other pneumothorax cases In many of the cases with no roentgenologic changes, the positive culture was present at the time of admission and was associated with the type of infiltration

As regards the sanatorium course after the positive culture, there was no change in 16, resolution in 10 (seven exudative-productive and three predominantly productive [exudative-productive]), progression in two (one exudative-productive and one pneumothorax), and one patient had progression, then resolution (predominantly productive [exudative-productive]) The roentgenologic changes after the positive culture were thus limited principally to the exudative-productive cases and consisted usually

TABLE 1
Group I—Roentgenologic Changes at Time of Positive Culture

Type of Infiltration	No of Cases	None	Resolution	Progression	Alteration in degree of Pneumothorax
1 Exudative-productive	11	8	3	0	0
2 Predominantly Productive (Exudative-productive)	8	5	3	0	0
3 Productive-Fibrotic	5	5	0	0	0
4 Pneumothorax	4	3	0	0	1
5 Pleural Effusion	1	1	0	0	0
TOTAL	29	22	6	0	1

of resolution In the productive-fibrotic cases there were no alterations in the lesion at the time of the positive culture or thereafter, indicating the lack of significance of the positive culture in these patients It was evident from the observations in this group that the tuberculous lesion could change much, though many sputum and gastric concentrates and cultures remained negative A single positive culture may also be of diagnostic importance and represent the only bacteriological evidence of tuberculosis

At the time of follow-up, i e., the final observation after sanatorium discharge, the patients were considered to be either in satisfactory condition or not A satisfactory status means negative sputum, good general condition, stable lesion and a full day's work tolerance (except in patients seen only a few months after discharge) Patients with at least two years' observation after leaving the institution would, if classified as satisfactory, be considered apparently cured An unsatisfactory status means progression of the lesion and/or positive sputum or rehospitalization

In Group I at time of follow-up, 20, or 69 per cent, were in satisfactory condition, six, or 20 per cent, unsatisfactory, two (7 per cent) had died, and one had an unknown status The six unsatisfactory cases included four of the exudative-productive group, one with pneumothorax, and one with pleural effusion The two deaths were pneumothorax cases The poor results in the patients admitted with pneumothorax are probably related to the fact that three of these four patients had contralateral infiltration which changed later

Concerning the period of follow-up, 12 patients were seen up to one year after discharge, 11 from one to two years, four from two to three years, and one at four and one half years (one case was not followed)

Group II—Patients with an occasional positive culture This group includes 44 patients with an occasional positive culture, though in 28 of these 44 cases, consecutive positives also occurred The total number of positives in every patient was less than half of all the cultures In this group 26 were males, 18 females, with the lesions moderately advanced in 27 and minimal in 17 The disease was unilateral in 28 and bilateral in 16 There was at least six months' sanatorium observation after the first positive culture, with the average stay 15.3 months All of the sputum and gastric concentrates in these patients were negative, a total of 1475 (939 sputum, 536 gastric), an average of 33.5 per patient There were 438 negative cultures (370 gastric, 68 sputum), an average of 9.9 per case, and 147 positive cultures (134 gastric, 13 sputum), an average of 3.3 per patient As regards positive cultures, there were

19 patients with 2 consecutive ones, five with three, one with four, and three with two and three successive positives

The roentgenologic changes associated with the positive cultures have been considered according to the type of lesion or treatment. These findings are outlined in Table 2.

In listing the findings in these patients with multiple positive cultures, the final outcome in the behavior of the infiltration was considered. Every individual positive culture was not associated with a change in the lesion but if with a series of positive cultures either resolution or progression occurred, the case was listed as such. The change may have taken place at any time during the sanatorium observation of the individual but must have been associated with the positive cultures. If no roentgenologic changes occurred with all of the positive cultures, the patient was classified under "None" in the table. If both resolution and progression were evident, that would be noted under a separate heading.

Of the 44 patients, the occasional positive cultures were associated with no roentgenologic changes in 16, or 36.3 per cent, resolution in 16, or 36.3 per cent, progression in three (6.8 per cent), resolution, then progression in four (9 per cent), pneumothorax in three (6.8 per cent), and alteration in degree of pneumothorax in two (4.5 per cent).

1) In each of the five patients with cavitation, positive cultures were associated with the admission lesion. Three had pneumothorax and their cultures remained positive while the pneumo-

TABLE 2
Group II — Roentgenologic Changes at Time of Positive Cultures

Type of Lesion	No. of Cases	None	Resolution	Progression	Resolution Then Progression	Pneumothorax	Alteration in Degree of Pneumothorax
Cavitation	5	0	2	0	0	3	0
Exudative-Productive with suspicious highlights	5	0	3	2	0	0	0
Exudative-Productive	14	2	8	1	3	0	0
Principally Productive (Exud -Prod)	5	2	3	0	0	0	0
Productive-Fibrotic	7	7	0	0	0	0	0
Pneumothorax	4	1	0	0	1	0	2
Thoracoplasty	4	4	0	0	0	0	0
TOTAL	44	16	16	3	4	3	2

thorax was partial and not selective, but with closure of the cavities, aided by intrapleural pneumonolysis, the cultures became and remained consistently negative. In the other two cases the cultures were positive while resolution continued with bed rest and became negative with final cavity closure. The sensitivity of the cultures and correlation with the changing lesions—resolution and cavity closure—is well demonstrated. The cultures also indicate the effectiveness of the pneumothorax, for only after selective collapse and control of the lesion do they become negative.

2) In the five patients with exudative-productive lesions and questionable annular areas, the cultures were positive with the infiltration and then changes occurred in the lesions and cultures. In two patients cavitation became definite, and after selective pneumothorax, the cultures were converted. In the other three the cultures continued positive while resolution of the infiltration took place and after disappearance of the suspicious highlights became negative. The persistence of positive cultures in the presence of an unchanged roentgenogram with suggestive highlights is significant. These cases should be considered active for the cultures warn of actual cavitation which may occur, or they remain positive with cavitation present and continue so with resolution until healing is definite.

3) In the 14 cases with exudative-productive lesions, the significance and sensitiveness of the positive cultures was indicated by the fact that they were associated with roentgenologic changes in all but two. Most commonly resolution occurred (eight cases), in three resolution then progression, and in one, progression. It is interesting and important to know that resolution can cause or be associated with positive cultures. Resolution, of course, indicates instability of the tuberculosis. As fibrosis became apparent, the positive cultures were less often associated with visible roentgenological changes. The cultures follow no definite pattern all the time. There may be no roentgenologic changes with an occasional positive culture and sometimes they precede or warn of an impending spread of the lesion or are associated with progression. Patients with positive cultures would need close observation, for with final stability of the infiltration, the cultures do become negative. One of these patients had pneumothorax and in this case two positive cultures occurred six months after therapy started and were of questionable significance.

4) There were five patients with principally productive (exudative-productive) lesions. In two, the positive cultures were unassociated with changes, while in the other three, slight resolution occurred. The cultures became negative as fibrosis was established.

5) Seven patients had productive-fibrotic infiltration although

in two the lesion had a moth-eaten appearance. All of the positive cultures occurred with no visible changes in the roentgenograms, and some of the patients were ambulatory with the positive cultures. Apparently in productive lesions an occasional positive culture can occur without significance.

6) In the four pneumothorax cases, the positive cultures were associated with alterations in the degree of collapse in two, with no roentgenologic changes in the third, and with definite resolution, then progression of the infiltration within the pneumothorax lung in the fourth. The presence of an occasional positive culture at intervals up to 15 months after initiation of the pneumothorax with slight changes in the degree of collapse may be of questionable significance, or indicate that healing within pneumothorax takes time or that the collapse should be altered to control the disease.

7) In the four postthoracoplasty cases, the positive cultures were unassociated with visible x-ray changes and were found at various intervals—up to 13 months after operation in two patients, and during the second year in the other two though fewer positives occurred the second year postoperatively. The healing process is apparently slow after thoracoplasty and the cultures are the last bacteriological specimens to become negative. With this gradual arrest of the disease an occasional positive culture can be expected, particularly during the first year and less often the second year after operation without indication of "malignant" or active tuberculosis. The cultures can be used to evaluate the end result of the operation as this cannot be determined from the roentgenogram alone.

At time of final observation, 31 of the 44 patients in Group II were in satisfactory condition (70.4 per cent), eight unsatisfactory (18 per cent) and five were not followed. The unsatisfactory cases included two of the exudative-productive, cavitation, and productive-fibrotic cases respectively and one of the pneumothorax and principally productive (exudative-productive) patients. The progressions in the productive-fibrotic cases occurred in the two with moth-eaten appearance of the lesion. It seems that while positive cultures may not be significant in frankly productive tuberculosis, in moth-eaten lesions they should be regarded as indicative of active disease. As regards the period of follow-up, five patients were not seen, 10 were observed up to one year after discharge, 21 from one to two years, five from two to three years, and three from four to five years.

We have also observed patients with an occasional positive culture where, in addition, one or more positive sputum or gastric concentrates were present. The positive cultures had the same significance as described for the Group II cases. However, in the

cases with progression, the positive cultures would often precede definite cavitation and the positive sputum concentrates. In patients given pneumothorax, the sputum concentrates would become negative first, the gastric concentrates next, and the cultures last.

Group III — Patients with a majority of cultures positive This group includes 34 patients. There were 22 females and 12 males, with lesions unilateral in 12, bilateral in 22, and moderately advanced in 25, minimal in six and far advanced in two. There was at least six months' sanatorium observation, though the average stay was 16 months. All sputum and gastric concentrates were negative. There was a total of 1099 negative concentrates (689 sputum, 410 gastric), an average of 33 per patient. The negative cultures totaled 156 (141 gastric, 15 sputum), or 4.7 per case. There were 294 positive cultures (274 gastric, 20 sputum) or nine per patient. The roentgenologic changes associated with the positive cultures are outlined in Table 3.

In every patient in this group roentgenologic changes occurred. This indicates that the more frequently the cultures are positive in any individual case, the greater the likelihood of unstable active tuberculosis. Moreover, progression was the end status of the lesion in 20 patients (59 per cent) and had also occurred in three others (9 per cent) before final resolution. Progression of the lesion took place more often in this group than in any other. Resolution occurred in 11 patients, or 32 per cent of the group.

1) Twenty-eight of the patients had exudative-productive lesions, though in 15 of them there were questionable areas of cavitation. In these cases the positive cultures were associated with the following changes: (a) In 11 the positive cultures were found

TABLE 3

Group III — Roentgenologic Changes Associated with Positive Cultures

Type of Infiltration	No. of Cases	None	Progression	Resolution Then Progression	Progression Resolution Then Progression	Resolution	Progression Then Resolution	Progression Resolution Then Progression
Exudative-Productive	28	0	11	5	2	9	1	0
Silico-Tuberc	1	0	0	0	0	1	0	0
Pneumothorax	1	0	0	0	0	0	1	0
Productive-Fibrotic	1	0	0	0	0	0	0	1
Cavitation	3	0	2	0	0	1	0	0
TOTAL	34	0	13	5	2	11	2	1

with the admission infiltration and then progression occurred at various intervals thereafter. The cultures, therefore, preceded progression but in four cases there was not an actual increase in the extent of the lesion but cavitation became definite (b) In five, resolution first took place and then progression occurred with definite cavitation apparent in one (c) In two there was a series of changes—progression, then resolution, and finally progression again. Therefore, in 18 of these 28 patients with exudative-productive lesions, progression or cavitation occurred ultimately with the positive cultures (d) In nine the positive cultures were present with resolution of the lesion. In several the resolution was only slight in extent (e) In one, slight progression was followed by resolution. Ten of these patients received pneumothorax while in the sanatorium (two of them bilateral). In nine of them the cultures became and remained negative after an effective anatomic collapse.

It should be emphasized that these positive cultures occurred as the only bacteriological evidence of tuberculosis, all the sputum and gastric concentrates being negative. Many roentgenologic changes occurred with the cultures (progression, cavitation, closure of cavities, resolution, and alteration in pneumothorax) showing their sensitivity as an indication of the instability of the lesions.

If cultures remain persistently positive with unchanged x-ray findings, questionable rarefaction or a lesion difficult to interpret because of atypical location, the tuberculosis should be considered active, for in many cases under these circumstances the positive cultures precede progression. Persistently positive cultures should be considered to have the same clinical significance as positive sputa. Even if the positive cultures are associated with resolution, (particularly if there are questionable annular areas) the tuberculosis may still be active for progression can follow resolution.

In 12 of these 28 cases bronchoscopies were done. Four patients were negative, two revealed mucopurulent pulmonary drainage, one a check-valve mechanism, three showed edema of the mucous membrane and two had granulomatous changes. It was not probable that these bronchial lesions alone caused the positive cultures as there was no bronchial ulceration or caseation.

2) In the patient with silico-tuberculosis (third stage silicosis) every culture was positive the first year and all but three were negative the second year. Although the x-ray showed little change with slight resolution, the cultures became negative. Because the silicosis was so massive, the healing of the tuberculosis was not obvious.

3) In the pneumothorax case the positive cultures were associated with no changes for a few months, then an annular area

became apparent As the collapse was increased the annular area disappeared

4) One patient had a productive fibrotic lesion The positive cultures preceded progression on two different occasions and resolution occurred after each spread With fibrosis established, the cultures finally became negative

5) Three patients were admitted with definite cavitation Extensive changes occurred with the positive cultures in each case and in two the cavities became larger, and in the third, the cavity closed

As regards follow-up of the 34 patients in Group III, 15 (44 per cent) were satisfactory, 11 (32 per cent) unsatisfactory, two (6 per cent) dead, and six were not reported All of the unsatisfactory results (except for one patient with cavitation) and the deaths were in the patients with exudative-productive lesions The follow-up results are poorer in this group with the majority of cultures positive than in any other group This again indicates that the more often the cultures are positive, the more probable the presence of active unstable tuberculosis The final observation occurred during the first year after discharge in 15 cases, from one to two years in six, from two to three in seven, and six were not followed

There have been many other cases seen in whom a majority of the cultures were positive as in Group III where in addition, positive concentrates were present for one to several months The conclusions concerning the correlation of the positive cultures and the roentgenologic changes in these patients are similar to those reached for the Group III cases However, other observations were also made In the patients with progression the positive cultures usually preceded the positive gastric and sputum concentrates On the other hand, with resolution or closure of cavitation by bed rest or collapse measures, usually the sputum concentrates became negative first, the gastric concentrates next, then the sputum cultures and finally the gastric cultures Occasionally, in thoracoplasty, the persistence of positive cultures may be due not to a slow healing process but an active lesion In one case a suspicious residual cavity was confirmed by tomography and positive sputum followed the positive cultures Persistently positive cultures in the presence of a good unilateral pneumothorax would often precede contralateral progression, and after bilateral pneumothorax, the cultures became negative Positive cultures with a poor pneumothorax collapse obviously meant active disease and preceded progression and positive concentrates In other words persistently positive cultures with pneumothorax could indicate uncontrolled tuberculosis in the pneumothorax lung or an on-coming contralateral spread

There has been an occasional exception to the statement that positive cultures lack significance in productive lesions. Occasionally in such patients with questionable annular areas or moth-eaten lesions, or characteristic productive infiltration with an observation period of many years, progression and positive sputum would occur.

Cultures are also important in their relationship to symptomatology and progression. There may be no symptoms prior to progression when the sputum is negative but the cultures positive, and this condition may continue for months. Symptoms will then appear only with the actual spread of the lesion. Therefore, the persistently positive cultures without symptoms being present indicate that the disease is unstable.

Discussion

We have tried to determine the significance of single, occasional and frequent positive cultures and to evaluate them in the general supervision and treatment of patients with tuberculosis. This is an important problem as there is no unanimity of opinion in the interpretation and practical application of positive culture reports. Some clinicians claim that cultures are too sensitive to be used as a guide in the treatment of tuberculosis and that they can be positive in many cases of tuberculosis without being significant and are associated with slight or unimportant changes in the lesion. We do not subscribe to this belief. We have outlined the circumstances under which little or much emphasis could be placed on positive cultures. There are other impressive reasons why culture examinations should be done as a routine laboratory procedure.

One of the factors that determines the significance of positive cultures is the frequency of the positive reports. A single or occasional positive culture may have little or no importance, but the more often the cultures are positive, the more significant they are of active disease. There were no roentgenologic changes associated with the positive culture in 76 per cent of the patients with a single positive culture (Group I), in 36 per cent of the patients with an occasional positive culture (Group II) but in none of those with a majority of the cultures positive (Group III). There are conditions described for Group II cases where even occasional positive cultures may be of consequence.

Positive cultures may occur under various circumstances: (a) as the only bacteriological evidence of tuberculosis, (b) with resolution of infiltration or increase of fibrosis, (c) prior to and with progression, (d) as indicative of unsuccessful collapse therapy, (e) with variations in the degree of pneumothorax, (f) with gradual healing in thoracoplasty and pneumothorax cases.

The presence of positive cultures should warrant extra roentgenologic and laboratory examinations (frequent and consecutive concentrates and cultures) Special studies like tomography might also be indicated to evaluate the lesion The additional information obtained will help determine the significance of the cultures

For a more accurate determination of the clinical status of the patient, both the cultures and roentgenograms should be considered important Some clinicians claim that more can be judged about the supervision of their cases by repeated roentgenograms than from cultures However, to use the roentgenograms alone may lead to mistakes in management and therapy This is not meant to belittle the value of x-ray findings as they are important, and in many cases, can even serve as the principal means of observation The cultures are, however, also necessary as they help in evaluation of the patient's condition and determination of prognosis and treatment

There are limitations in the use of cultures The cultures are not necessarily correlated with the x-ray findings There may be roentgenologic changes with negative cultures and no changes with positive cultures On the other hand, in many of our cases, particularly Groups II and III, roentgenologic changes occurred with all sputum and gastric concentrates negative and only the cultures positive The alteration in the lesion may be gradual or rapid, with ultimate definite resolution or progression yet the roentgenogram may be the same with many of the positive cultures

The presence of positive cultures without roentgenologic changes may be due to the fact that alterations in the lesion do occur that are not discernible by x-ray examination It has also been noted (Amberson) that small calcific areas may appear in lung parenchyma formerly considered normal, indicating that healing had taken place in lesions that had not been observed Sometimes lesions may also be hidden from view

Although cultures are so sensitive that they may be positive with resolution, patients do finally become negative with stability of the tuberculosis achieved by rest or effective collapse measures Without the use of routine cultures the appearance of progression and other roentgenologic changes may be unexpected and come as a surprise The cultures are sensitive and can warn of oncoming changes and indicate instability of the lesion and active tuberculosis Positive cultures in spite of negative sputum, an unchanged x-ray, or even resolution, may precede progression of the lesion If the cultures are considered with importance the patient will be observed carefully and without an increase of exercise until the status of the lesion has been determined Other-

wise with disregard of the cultures and the patient kept ambulant, progressions may occur which could have been prevented

Cultures also help to indicate therapy Treatment may not be too difficult to determine when, even with the sputum negative, the positive cultures are associated with a lesion evidently active or progressive But if the roentgenograms are unchanged persistently positive cultures may still indicate rest or collapse therapy as the cultures can be more expressive of alterations in the lesion than the x-ray If the infiltration is not visualized clearly within a collapsed lung, the cultures can help determine the efficacy of the treatment From the roentgenogram alone one could not know the end result or value of the therapy

In addition to changes in the lesion due to tuberculosis, intercurrent bronchopulmonary infections of a nontuberculous nature may disturb a quiescent pulmonary tuberculous focus and cause a temporary appearance of tubercle bacilli In almost all of the productive-fibrotic lesions the positive cultures, even when frequent, seemed to have little significance because of the lack of immediate or late changes in the infiltration

Because of the findings in this study we would suggest that the criteria of the National Tuberculosis Association for the discharge of patients from tuberculosis institutions should be modified to require the routine use of culture examinations and to have them negative before classification of patients as arrested Patients may have unchanged x-ray findings for a period of months with sputum and gastric concentrates negative and therefore be considered stable, and then progression may occur A more accurate idea of the status of the case could be determined by the utilization of cultures Positive cultures, during an apparent period of stability, may warn of unstable disease or impending changes, while negative cultures would indicate the true condition of arrest

CONCLUSIONS

This is a study of 107 cases with all sputum and gastric concentrates negative and only cultures were positive The patients have been considered in three groups those with a single, occasional, or majority of the cultures positive We have observed other patients with a similar grouping of positive cultures who also had occasional positive sputum or gastric concentrates The positive cultures have been correlated with the type of infiltration, roentgenological changes, clinical condition, course of the disease, treatment, other laboratory findings and the period of follow-up observation

Conclusions concerning the significance of the positive cultures as related to the factors mentioned above have been presented

CONCLUSIONES

Es este un estudio de 107 casos en los cuales todos los concentrados del esputo y del contenido gástrico fueron negativos y sólo los cultivos fueron positivos. Se han considerado a los pacientes en tres grupos: aquellos que resultaron positivos en sólo un cultivo, en unos pocos cultivos o en la mayoría de los cultivos. Hemos observado otros grupos semejantes de pacientes con cultivos positivos que, ocasionalmente, también tenían positivos concentrados del esputo o del contenido gástrico. Se han correlacionado los cultivos positivos con el tipo de infiltración, alteraciones ionto-genológicas, condición clínica, evolución de la enfermedad, tratamiento, otros hallazgos de laboratorio y el período de observación subsecuente.

Se han sacado conclusiones acerca del significado de los cultivos positivos en relación a los factores mencionados.

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D I S C U S S I O N

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The results of Dr. Bobrowitz's study respecting the significance of positive cultures in the prognosis of pulmonary tuberculosis are in agreement with those of Dr. Chang of Rutland State and Dr. Abeles of the Montefiore County Sanatorium. They substantiate what physicians have known from practical experience for many years, namely, that all else being equal, the prognosis of patients with pulmonary tuberculosis who eliminate tubercle bacilli on rare occasion is infinitely better than of those who expectorate tubercle bacilli continuously or even intermittently.

With refinements in techniques of sputum examinations, arbitrary divisions between relative paucity or richness of bacilli in the sputum, depending on the methods used, are becoming increasingly more academic. We know that seldom does one fail to isolate tubercle bacilli in patients with active pulmonary tuberculosis. The practical problem is how are we to evaluate the sig-

nificance of sputum examinations in the management of individual patients. Should one adopt the fatalistic attitude expressed by one of our English colleagues to the effect that a patient with pulmonary tuberculosis cannot be said to be cured of his disease until he is safely dead or shall we adopt the policy of neglecting the occasional occurrence of acid-fast organisms if the patient is in good condition and the x-rays reveal stabilized disease?

I believe a satisfactory solution is feasible on the basis of established facts. If a patient has tubercle bacilli in the sputum or gastric contents, either on direct smear or in the *majority* of cultures, that individual should be treated as one with active pulmonary tuberculosis. If acid-fast organisms are found only in a *minority* of the cultures, the patient's status may be considered quiescent depending on other factors such as the age, the existence of an apparently adequate collapse of the lung, the appearance of the x-ray films, and constitutional signs. In the assessment of this particular group, careful note should be made whether or not these patients have recently had streptomycin with its known temporary suppressive effect on the tubercle bacillus. Patients who show acid-fast organisms on culture *on rare occasion after a lapse of two years*, during which time most reactivations of tuberculosis take place, should be considered as having the disease arrested. The term "arrested" should be retained in our nomenclature because of the important effect it has on patients' morale. After a patient has chased the cure for two years, a physician should have something else to offer him than to say the disease is inactive. The significance of occasional cultures can be explained at this time as well as the importance of having periodic chest examinations. The classification proposed is practical. It does not minimize the significance of the occurrence of rare tubercle bacilli in patients with clinically arrested disease. At the same time, it takes into consideration the fact that the final decision depends on a review of the entire status of the individual patient rather than on the results of the bacteriological examinations alone.

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In any case of tuberculosis, our rationale of treatment must be based on our concept of the nature of the pathology and the inherent quality of response of the patient's tissue to the invading germ. A clear knowledge of the existing disease gives some clue as to its future natural history. A productive lesion has been shown from experience to be relatively benign while a caseous one is more malignant. The whole background is colored by the patient's

reactivity or resistance to the disease Unfortunately for an exact evaluation of some of these factors, the disease process is usually subsurface and not available for direct examination We are forced, therefore, to rely upon indirect methods, chief of which are x-ray and sputum studies

Our image of the underlying disease can only be as accurate as our indirect methods of examination X-ray study is an admirable example of this hypothesis As the exactness of our examination has improved, so has our knowledge of the pathological process Tomography now reveals cavity which was formerly unsuspected and serves to explain some of the previously baffling courses of the disease Sputum studies have likewise become more exact with our advancement in technique Concentration methods reveal bacilli where plain smears were negative Cultural methods still further perfect our search beyond the concentration technique and Dr Bobrowitz has added statistical proof in support of its value

The purpose of these studies, of course, is to tell us the nature of the underlying pathology and its progress toward healing or otherwise The presence of bacilli in the sputum obviously means caseation When many bacilli are present, it is probable that the area of caseation is relatively large Conversely, few bacilli indicate a relatively small area of caseation and true disappearance of the organisms must mean healing The presence of free bacilli in the bronchial tree is significant not only as an indicator of the type of pathology and its state of healing but also as a prognosticator of future events The increasing incidence of relapse in proportion to the increasing frequency of positive cultures as shown by Dr Bobrowitz is extremely significant

The therapeutic course which the clinician will follow in the individual patient whose sputum is positive on culture and negative by other methods of study must be guided by his concepts of the underlying pathology, the efficacy of the available methods of treatment, and the patient's ability to cope with his infection No two patients are exactly alike As always the treatment must be tailored to fit the individual pattern It is not within my scope to further discuss this angle Suffice to say that anything which improves our ability and accuracy in reaching this decision is bound to be of value to the patient Sputum cultures are in this category and should be made use of wherever possible

Fibromyxoma of Pleura Report of Case

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As far as we have been able to determine, 31 cases of giant subserous areolar-tissue tumor of the pleura have been reported in the literature To the best of our knowledge, Neumann¹ has reported the only case in which such a tumor occurred in a child We shall report another case in which this type of tumor occurred in a child

REPORT OF CASE

A white girl, aged 2 years, was brought to the Evangelical Hospital, in Chicago, Illinois, on January 14, 1948, because of acute respiratory symptoms and anorexia of three weeks' duration At birth, her color and cry had been good She had weighed eight pounds and two ounces (3.7 kg) at birth and 18 pounds and 6 ounces (8.25 kg) at the end of six months Her development had been normal, she had sat up at five to six months, had stood at 10 months, had walked at 12 months, and had talked at 14 months She had had chicken pox at the age of one year During the second year, her health apparently had been good She had not been taken to the family physician for fourteen months before she was brought to the hospital

Physical Examination The patient was a fretful, well developed child who weighed approximately 30 pounds (13.6 kg) The rectal temperature was 103.8 degrees F (39.9 degrees C) The respirations were short and shallow, and the respiratory rate was 40 per minute

Inspection of the thorax disclosed an increased antero-posterior diameter, widening of the interspaces, and decreased expansion on the left side Tactile fremitus was absent on the same side The percussion note was flat to dull over the entire left side of the thorax, whereas hyperresonance was present over the lateral portion of the right side Auscultation revealed absence of breath sounds over the left side, except along the sternal border and in the supraclavicular space, where distant vesicular breathing was audible

The apical impulse of the heart was palpable in the right xiphocostal angle Auscultation of the heart disclosed a regular rhythm and a rate of 130 beats per minute The heart sounds were audible only to the right of the sternum The liver could be palpated easily, but the spleen was not palpable The physical examination did not disclose any other significant abnormality

Laboratory Data The urine was normal The erythrocyte count was 4,500,000 and the leucocyte count varied between 12,400 and 17,500 per cubic millimeter of blood, respectively The concentration of hemoglobin was 11.5 gm per 100 cc of blood The percentage distribution of the leucocytes was as follows polymorphonuclear neutrophils, 60 per cent, lymphocytes, 30 per cent, and monocytes, 10 per cent The sedimentation

rate of the erythrocytes was 27 mm in one hour (Westergren's method) The results of Vollmer's patch test for tuberculosis and Kahn's test for syphilis were negative No sputum was available for examination

Roentgenograms of the thorax were suggestive of a massive pleural effusion on the left side, which had displaced the trachea, mediastinum and heart to the right, and had produced partial atelectasis of the right lung (Fig 1)

Clinical Course The patient did not show any evidence of improvement during the 13 days that she was in the hospital Her temperature fluctuated between 97.8 and 99.8 degrees F (36.6 and 37.7 degrees C) The pulse rate varied between 110 and 140 and the respiratory rate ranged between 30 and 40 per minute, respectively Because of the presence of severe cyanosis, the patient was placed in an oxygen tent and 100 per cent oxygen was administered Twenty-five thousand units of penicillin, in the form of an aqueous solution, were administered intramuscularly, every three hours The cyanosis recurred only when the administration of oxygen was discontinued while the patient was being examined

On two different days, thoracentesis was attempted in the fifth, sixth, seventh and eighth interspaces posteriorly and laterally on the left side, but yielded only a few drops of blood The trocar transmitted the sensation of probing solid tissue On the assumption that the patient had an intrathoracic neoplasm, she was transferred to the chest service at the Wesley Memorial Hospital on January 26, 1948 Cyanosis and dyspnea were present when the patient was admitted to this hospital, and thoracentesis yielded about 3 cc of blood, which did not contain any tumor cells The signs of respiratory distress increased, and the patient died on the evening of the day of admission

Necropsy Necropsy was performed under the supervision of Dr Thomas C Laipply, Associate Professor of Pathology, Northwestern University School of Medicine, and pathologist at the Wesley Memorial Hospital



FIGURE 1



FIGURE 2

Fig 1 Displacement of heart and trachea to right and compression of right lung due to expansive growth of left pleural tumor—Fig 2 Loose fibroblastic connective tissue with stellate cells intermixed with more compact darker staining cellular areas hematoxylin and eosin stain ($\times 420$)

TABLE 1 Data in 32 Reported Cases of Giant Tumor of the Pleura

Case	Author	Date	Country	Age yrs	Sex	— SIZE OF TUMOR —		SITE OF ORIGIN		Pathologic Diagnosis
						Dimensions cm	Weight gm	Thorax	Pleura	
1	Feron ²	1862	France	24	F	10,000				Fibroma
2	Kahler ³	1882	Bohemia	53	F	20 by 20 by 12		Right	Visceral	Fibroma
3	Kidd and Habershon ⁴	1898	England	18	F			Left	Visceral	Myxosarcoma
4	Podack ⁵ (case 3)	1899	Germany	53	M	33 by 20 by 15		Left	Visceral	Fibrosarcoma
5	Israel-Rosenthal ⁶ (case 1)	1900	Norway	19	M	20 by 15		Right	Visceral	Round-cell sarcoma
6	Schmidt ⁷	1903	Germany	53	M	9 by 5 by 4		Left	Visceral	Fibroma
7	Torri ⁸ (case 3)	1905	Italy	67	F			Right	Visceral	Sarcoma
8	Henke ⁹	1906	Germany	70	F	Size of child's head				Sarcoma
9	Mehrdorf ¹¹ and Braun ¹⁰	1908	Germany	43	F	25 by 11 by 19	3,270	Right	Parietal	Fibrosarcoma myxomatoides
10	Ricard ¹²	1908	France	Young	F		6,000	Left		Sarcoma
11	Garre and Quncke ¹³	1912	Germany	49	M	11 by 12 by 4, 17 by 14 by 6*	1,250	Left	Parietal	Spindle-cell and round-cell sarcoma
12	Dorendorf ¹⁴	1914	Germany	51	F	25 by 24 by 16	2,900	Left	Parietal	Fibrosarcoma
13	Rosenberger ¹⁵ (case 1)	1916	Germany	65	F			Left	Parietal	Round-cell sarcoma
14	Pallasse and Roubier ¹⁶ (case 2)	1916	France	51	F		2,200	Left	Parietal	Malignant fibroma
15	Palasse and Roubier ¹⁶ (case 3)	1916	France	59	M	30 by 20	5,100	Right	Parietal	Benign fibroma

16	Schneider ¹⁷	1924	Germany	73	F	15 by 9 by 6	Left	Parietal	Fibrosarcoma
17	Nevinny ¹⁸	1927	Germany	43	F		Right	Visceral	Sarcoma
18	Sala ¹⁹	1930	United States	40	F		Right	Parietal	Fibrosarcoma
19	Klemperer and Rabin ²⁰ (case 1)	1931	United States	48	F	16 by 15 by 7	Left	Visceral	Fibrosarcoma
20	Klemperer and Rabin ²⁰ (case 2)	1931	United States	53	M		Left	Visceral	Spindle-cell myxosarcoma
21	Klemperer and Rabin ²⁰ (case 3)	1931	United States	50	F	19 by 10 by 10	Right	Visceral	Embryonic connective- tissue tumor
22	Lichtenstein ²¹	1931	Germany	50	M	18 by 11, 5 by 4†	Left	Parietal or Visceral	Sarcoma
23	Unger ²²	1932	Germany	55	F	27 by 20 by 14	Right	Parietal	Fibroma
24	Cabot ²³ Case No 18452	1932	United States	55	M		Left	Parietal	Fibrosarcoma
25	Lyssunkin ²¹	1933	Germany	19	F	19 by 14	Right	Visceral	Sarcoma
26	Neumann ¹	1933	Germany	2¾	F		Left	Parietal	Sarcoma
27	Mintz ²⁵	1935	United States	64	F	15 by 25 by 8	Right	Parietal	Fibroma
28	Farwceit ²⁶	1945	England	48	M		Right	Visceral	Fibroma
29	Belleville ²⁷	1945	Argentina	53	M	26 by 20 by 8	Left	Visceral	Fibroma
30	Fernandez Luna ²⁸	1946	Argentina	60	M	26 by 16 by 16	Left	Visceral	Fibrosarcoma
31	McNamara Sargent and Costich ²⁹	1947	United States	55	M	28 by 16 by 14	Left	Parietal	Sarcoma
32	Hauch and Sittler	1949	United States	2	F	17 by 10 by 8.5	Left	Parietal	Fibromyxoma

*Tumor presumably removed in 2 sections

†Tumor removed in 2 sections

It disclosed that the left side of the thorax was completely filled by a large firm mass which had compressed the left lung markedly and had pushed all of the mediastinal structures, including the heart, to the right of the midline. There were many fibrinous adhesions between the mass and the parietal pleura and between the edges of the compressed visceral pleura and the mass. The mass was well encapsulated in a smooth glistening membrane. It was ovoid in shape, weighed 1,190 gm, and measured 17 by 10 by 8.5 cm. The external surface was slightly lobulated in appearance. In the upper pole of this mass there was a cyst which measured 3 by 4 cm and contained clear, dark, greenish yellow fluid. The wall of the cyst was of moderate consistency and resistance to section and was 0.1 cm thick.

The left lung was compressed against the medial and posterior surfaces of the mass. Neither lobe crepitated when palpated. The lobes of the right lung were firmer than normal. Palpation of these lobes revealed a moderate decrease in crepitation.

Microscopic examination revealed that the tumor was composed of embryonic connective tissue. In some areas, the cells were stellate and contained a great deal of myxomatous material, in other areas, the cells were compact and markedly basophilic. A few mitotic figures were observed. Hemorrhage and slight necrosis were observed in some sections. The final anatomic diagnosis was as follows: fibromyxoma of the parietal mediastinal pleura on the left side of the thorax (Fig. 2), slight bronchopneumonia of both lungs, and marked atelectasis of the left lung.

Comment

Modern advances in thoracic surgery have stimulated clinicians to consider the possibility of giant pleural tumors in the differential diagnosis of diseases of the thorax. Consequently, reports of such neoplasms have become more frequent and their study has been more thorough. The geographic distribution of reported cases has also shifted decidedly in the past two decades. Of the nine cases of giant tumor of the pleura which were reported from 1908 to 1927, inclusive, all were reported in the European literature, of the 15 cases that have been reported subsequently, 10 were reported from the Americas and 5 from Europe (Table 1).

Operation was performed in two of the 17 cases which were reported prior to 1928. In both of these cases, the patients survived. Thoracotomy was performed in five of the 15 cases which have been reported since 1928. In one of the five cases, the patient died in the hospital. If large tumors of the pleura are not excised, they continue to grow and eventually interfere with the pulmonary circulation and cause anoxic anoxia.

Giant connective-tissue tumors of the pleura affect females more frequently than they affect males. In the 32 reported cases, including the case which we have just reported, 62.5 per cent of the patients were females and 37.5 per cent were males. The incidence was highest in persons in the sixth decade (Table 2).

These tumors of the pleura have three interesting features:

(1) clinically, they resemble a massive pleural effusion, (2) they originate in various portions of the pleura, and (3) although the clinical signs and symptoms and the macroscopic appearance indicate that these tumors are benign, histologic examination, usually, indicates that they are malignant

A large pleural tumor filling one side of the thoracic cavity presents a clinical and roentgenologic picture of massive pleural effusion. In two thirds of the cases under consideration, pleurocentesis was attempted but fluid was obtained in only one case. The trocar usually felt as though it was imbedded in solid tissue, and Garre asserted that this feeling was so characteristic as to be diagnostic.¹³

Pathologists have invariably discovered numerous loose attachments between these giant pleural tumors and the costal, mediastinal, diaphragmatic, pericardial and visceral pleurae, hence, they have encountered difficulty in specifying the exact points of origin. The primary sites of the neoplasms reported in the literature were equally distributed between the visceral and parietal layers of the pleural membrane, and were encountered more often on the left side (60.0 per cent) than on the right side (40.0 per cent) of the thorax (Table 1). Feron,² Henke,⁹ and Ricard¹² failed to establish the sources of origin of the huge tumors in their cases. Lichtenstein²¹ felt that the growth he described could have arisen from either the mediastinal or visceral pleura. In the case reported herein, the prosector found fibrinous adhesions between the tumor and both the parietal and visceral surfaces of the pleura. According to Rokitsansky³⁰ and Clagett and Hausmann³¹ a tumor which does not possess a pedicle or is not attached to the pleura by dense fibrous bands must be considered to have become para-

TABLE 2
Age of Patients by Decades in Cases of Giant
Connective-Tissue Tumors of the Pleura

Age in Years	C A S E S	
	Number	Per cent
0 to 9	2	6.5
10 to 19	3	9.6
20 to 29	1	3.3
30 to 39	0	
40 to 49	6	19.4
50 to 59	13	41.8
60 to 69	4	12.9
More than 70	2	6.5

sitic within the pleural cavity. As the exact site of origin of these pleural tumors was often problematical at necropsy, it must be expected that their relationship to adjoining structures and their attachments would be even more difficult to delimit during thoracotomy. Hence, conclusive evidence is lacking as to whether or not the huge tumors reported by Doege,³² Susman,³³ and Clagett and Hausmann³¹ arose from the pleura or within the mediastinum. In Belleville's²⁷ case, pleuroscopy suggested that there was a pedicle attached to mediastinal structures, but subsequent surgical excision revealed that the pedicle arose from the hilum of the lung.

That these neoplasms might be clinically and macroscopically benign but histologically malignant was first suggested in the earlier German literature, and was confirmed by Nevinsky,¹⁸ Klemperer and Rabin,²⁰ and Lichtenstein.²¹ The last author classified pleural tumors into three groups. The first two groups included tumors that were frankly malignant, and the third was composed of the "benign" giant tumors of the pleura. According to Table 1, the tumors were histologically malignant in 22 (68.7 per cent) of the 32 cases. Nevertheless, all the tumors were well encapsulated and did not metastasize or invade the surrounding tissues. Kaufmann³⁴ and Brunner³⁵ have each reported a case of a huge localized neoplasm of visceral pleural origin which had metastasized.

In 1933, Neumann¹ reported a case in which the patient was a girl, 2 $\frac{3}{4}$ years of age. The symptoms and the laboratory, roentgenologic and postmortem findings in this case were similar to those in the case which we have reported in this paper. Except for the loss of weight, the palpable spleen and the clubbing of the fingers, the physical findings in his case were similar to those in our case. Neumann stressed the significance of the flat percussion note together with the firm fixation of the trocar between the ribs as clinical evidence of a dense pleural mass. Although the results of the first pleurocentesis were negative, a second puncture yielded a few particles of tissue which, microscopically, were composed of spindle cells and atypical giant cells. The final pathological diagnosis in his case was spindle-cell sarcoma of the left costal pleura. The tumor had filled the left thorax and had compressed the mediastinum to the right side, but it had not metastasized.

SUMMARY

This paper is based on the report of a case of giant localized, connective-tissue tumor of the pleura in which the patient was a girl, aged 2 years. As far as we have been able to determine, this is the second report of a case in which this type of tumor

has occurred in a child. It is evident that more cases of this tumor have been reported in the past two decades than had been reported previously. If these tumors are not excised, they will continue to grow and will impede the function of vital organs within the thorax. The possible presence of large tumors of the pleura must be considered in the differential diagnosis of diseases of the thorax which simulate massive pleural effusion. The site of origin of these growths appears to be subserous areolar tissue of either the parietal or visceral pleura. Although clinically they are benign, these neoplasms are usually histologically malignant. This case re-emphasizes the need for frequent periodic physical and roentgenographic examinations to detect the presence of unusual but fatal lesions during their early asymptomatic phase.

RESUMEN

En este trabajo se refiere un caso de un gigante tumor localizado del tejido conectivo de la pleura, en una niña de 2 años. Hasta donde hemos podido averiguar, éste es solamente el segundo caso referido de este tipo de tumor que haya ocurrido en un niño. Es evidente que se ha informado sobre un mayor número de casos de este tumor en las dos últimas décadas que en todo el tiempo anterior. Continúan creciendo estos tumores si no se los extirpa, hasta que llegan a impedir el funcionamiento de órganos intratorácicos vitales. En el diagnóstico diferencial de enfermedades del torax que se asemejan a derrames pleurales masivos, debe considerarse la posible presencia de grandes tumores de la pleura. Se cree que estos tumores se originan en el tejido aerolar subseroso de la pleura visceral o parietal. Aunque clínicamente son benignos, histológicamente estas neoplasias generalmente son malignas. Recalca de nuevo este caso la importancia de hacer frecuentes exámenes físicos y roentgenográficos para descubrir la presencia de raras, pero fatales, lesiones durante el período asintomático temprano.

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The Transpleural Endoscopic Approach to the Autonomic Nervous System and Its Therapeutic Possibilities*

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Operations on the thoracic sympathetic chain, as in hypertension for example, can be performed simply and without operative risk. After the induction of a pneumothorax, the entire sympathetic trunk, from the caudal portion of the stellate ganglion down to its passage through the diaphragm including its branches to the splanchnics and the rami communicantes, can easily be seen with a thoracoscope, shining through the parietal pleura. Although every anatomical atlas shows these topographical relations, until now this simple route has not been described. After death the parietal pleura quickly thickens and clouds like the cornea so that in the cadaver where new operative procedures are usually tried the vagus and sympathetic are no longer clearly seen. On the other hand, in open thoracotomies the reflex hyperaemia and the brilliant lighting of the operative field obliterates nuances. This may appear paradoxical, but it is the endoscopic illumination that brings out in rich contrast and relief the vegetative nervous system.

By means of thoracoscope and through either one or two openings in the thorax, the sympathetic can be injected or divided by cautery at any given point above the diaphragm. With a suitable instrument exeresis can be done and the nerves from below the diaphragm evulsed. This is not true of the vagus. The upper half is approachable with a direct optic and cautery. The lower half can be reached only at certain points and then with a 90 degree or 135 degree optic and a curved cautery.

In a series of 200 operations no complications were observed, with the exception of three intercostal neuralgias. The procedure is so easily performed that in some patients on the same day and even in the same hour the operation can be done first on the one and then on the other side. The advantages of the endoscopic method are:

- 1) There is practically no operative risk.
- 2) The procedure can be repeated. For example, a preliminary novocain block can be done, the therapeutic effects studied, and

*From the Surgical Clinic, University of Innsbruck, Innsbruck, Austria

after several days or weeks, a permanent interruption performed. Again as in hypertension with renal involvement, the first intervention (on the splanchnicus) eliminates the vasoconstriction of the kidneys. After an improved renal blood flow and function, the second intervention against the sympathetic can be carried out if necessary.

3) The operation can be performed with a certainty of exact localization, without general anesthesia, and without preliminary sedation, so that many new physiopathologic observations are possible.

In a short communication no discussion of the uses of this method as in hypertension, diseases of the liver, and biliary tract, pancreas, spleen and hemopoietic system, circulatory disturbances, bronchial asthma, and pulmonary tuberculosis can be made.

We wish only to note here that in our treatment of peptic ulcer we interrupt the sympathetic and not the vagus. This treatment will be discussed in another communication.

REFERENCE

- Kux, E *Ars Medici*, 1948, 676
 Acta Chirurg Belgica, 1948, 285
 dtische Mediz Wochenschr, 1949, 753
-

First International Congress on Diseases of the Chest

The First International Congress on Diseases of the Chest, to be sponsored by the American College of Chest Physicians in cooperation with the Forlanini Institute of Rome, will take place in Rome, Italy, in September, 1950. Dr. Attilio Omodei Zorini, Medical Director of the Forlanini Institute, will serve as chairman of the arrangements committee for the Congress. A scientific program covering all phases of diseases of the chest will be presented, as well as an x-ray conference, a motion picture session, round table discussions, and scientific exhibits. Physicians interested in presenting papers at the Congress are invited to submit titles and abstracts of their material to the program committee for consideration. Please send the information to the Executive Offices of the College, 500 North Dearborn Street, Chicago 10, Illinois.

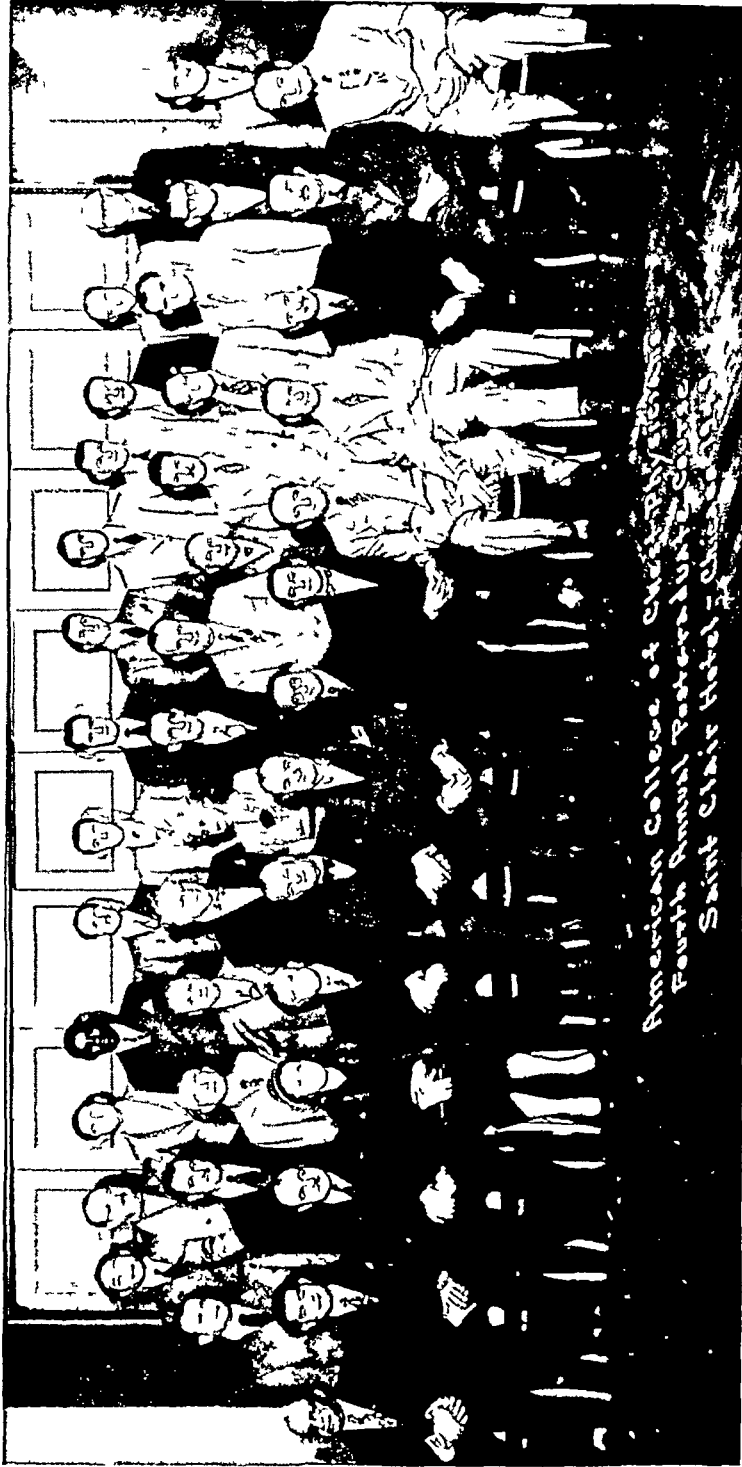
Fourth Annual Postgraduate Course Held in Chicago

The Fourth Annual Postgraduate Course in Diseases of the Chest was presented in Chicago during the week of September 19-23. There were 38 physicians registered for the course representing 17 states and Canada. Dr. Edwin R. Levine served as chairman of the postgraduate course committee with Drs. Paul H. Holinger, Minas Joannides, Darrell H. Trumpe, and Italo F. Volini as members. The committee plans to arrange a similar course in the fall of 1950 to be held in Chicago.

On Thursday evening, September 22, a dinner was held for the instructors and physicians who participated in the course. A photograph of the group may be found on page 628 of this issue of the journal. Dr. J. Winthrop Peabody, Washington, D. C., Chairman of the Council on Postgraduate Medical Education of the College, served as Toastmaster at the dinner and Dr. Richard C. Benkendorf, Bushnell, Illinois, made a brief talk as Valedictorian of the postgraduate class. The physicians who attended the course were as follows:

†Lamar E. Alford, M.D., Cairo, Illinois, John M. Baker, M.D., Columbus, Ohio, E. G. Cada, M.D., Downey, Illinois, Charles A. Castle, Comdr. USN, Great Lakes, Illinois, Ger. Au Chan, M.D., Farmingdale, N. Y., R. C. Benkendorf, M.D., FCCP, Bushnell, Illinois, Raymond C. Comstock, M.D., Louisville, Kentucky, R. P. Empey, M.D., Hamilton, Ontario, *J. M. Filiatrault, M.D., Montreal, Canada, Charles A. Freund, M.D., Chicago, Illinois, Stanley M. Gates, M.D., Little Rock, Arkansas, Allen W. Glinert, M.D., Chicago, Illinois, Morton N. Goldberg, M.D., Fort Worth, Texas, Harry M. Hepperlen, M.D., Beatrice, Nebraska, V. H. Hill, M.D., FCCP, Mobile, Alabama, Curtis R. Hoffman, M.D., Richmond, Indiana, George B. Kimbrough, Lt. (jg), USN, Great Lakes, Illinois, Philippe Landry, M.D., Montreal, Canada, John T. Lane, M.D., Biloxi, Mississippi, Paul V. Ledbetter, M.D., Houston, Texas, †Elizabeth A. Leggett, M.D., Ahwah-Ching, Minnesota, C. L. Lindo, M.D., Chicago, Illinois, Harry H. McCarthy, M.D., Omaha, Nebraska, *D. W. McCauley, M.D., Okmulgee, Oklahoma, H. N. McClelland, M.D., New Castle, Indiana, M. L. McClung, M.D., Indianapolis, Indiana, J. A. Muggly, M.D., Madison, South Dakota, Donald J. Schissel, M.D., Des Moines, Iowa, William W. Stead, M.D., Minneapolis, Minnesota, Paul W. Sunderland, M.D., Gibson City, Illinois, Frank Ryder Trigg, M.D., Norfolk, Virginia, †Raymond P. Wiesen, M.D., Milwaukee, Wisconsin, Carryl W. Wiggins, M.D., Oklahoma City, Oklahoma, J. R.

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Some of the physicians and instructors who participated in the Fourth Annual Postgraduate Course in Diseases of the Chest of the American College of Chest Physicians

Winston, M D , Temple, Texas, Russell S Wolfe, M.D , Houston, Texas, David C Wu M D , Kansas City, Missouri, Marion T Yates, Comdr , USN, Great Lakes, Illinois, George Zubowicz, M.D , Manteno, Illinois

*Associate Fellow, American College of Chest Physicians
†Associate Member, American College of Chest Physicians

College Chapter News

MICHIGAN CHAPTER

The Michigan Chapter of the College met coincident with the Michigan State Medical Society Annual Convention at Grand Rapids, September 22 A very informative, instructive and highly interesting meeting was held The dinner was followed by a talk on "Physiology of Pneumococcosis" by Dr George W Wright of Saranac Lake, New York His talk was followed by a discussion of the paper by Dr Oscar A Sander of Milwaukee, Wisconsin, who also made pertinent remarks of great value on dust disease in general and especially siderosis

The meeting was well attended by the members of the Michigan Chapter of the College and other members of the Michigan State Medical Society, totaling approximately 100 By special invitation a large group of industrial physicians were guests

C P Mehas, M D , Secretary-Treasurer

ROCKY MOUNTAIN CHAPTER

The Annual Meeting of the Rocky Mountain Chapter of the College was held Tuesday, September 20, in the Brown Palace Hotel, Denver, Colorado An interesting program was presented which was attended by more than 80 members and guests The business session and election of officers were held after the luncheon meeting and the following officers were elected for the ensuing year

Fred Harper, M D , Denver, Colorado, President

Robert C Cook M D , Fort Logan, Colorado, First Vice-President

H M Van Der Schouw, M D , Wheatridge, Colo , Second Vice-President

W Bernard Yegge M D , Denver, Colorado Secretary-Treasurer

WISCONSIN CHAPTER

The Wisconsin Chapter of the College held its Fifth Annual Meeting at the Schroeder Hotel, Milwaukee, Wisconsin on Sunday October 2nd The State Medical Society of Wisconsin held its annual meeting in Milwaukee October 3-5

The following program was presented at the chapter meeting

1 30 p m Registration

2 00 p m Scientific Session

'Antibiotics in the Treatment of Non-Tuberculous Diseases of the Chest

Wallace E Herrell M D Associate Professor of Medicine Mayo Foundation University of Minnesota Consultant in Medicine Mayo Clinic Rochester Minnesota

Etiology of Pulmonary Heart Disease

Chauncey Maher M D Associate Professor of Medicine Northwestern University Medical School Professor of Medicine, Post-graduate School of Medicine Cook County Hospital Chicago, Ill

"Surgical Management of Intractable Bronchial Asthma,"

John B. Grow, M.D., F.C.C.P., Chief, Thoracic Surgery, National Jewish Hospital, Denver, Branch Section Chief, Thoracic Surgery, Branch 13, U. S. Veterans Administration, Denver, Colorado

"Unusual Findings in Asymptomatic Chest,"

George M. Landau, M.D., Professor of Roentgenology, Postgraduate School of Medicine, Cook County Hospital, Chicago, Illinois

"Lymphomatoid Disease of the Chest,"

John S. Hirschboeck, M.D., Dean, Marquette University School of Medicine, Milwaukee, Wisconsin

"Pulmonary Manifestations of Collagen Disease"

D. Murnay Angevine, M.D., Professor of Pathology, Chairman, Dept. of Pathology, University of Wisconsin Medical School, Madison, Wis

College News Notes

Dr. Darrell H. Trumpe has been appointed Medical Director of Saint John's Sanitarium, Springfield, Illinois, and Dr. Jesse A. Stocker serves as Assistant Medical Director of the Sanitarium

Dr. Lamar A. Alford, formerly at Stony Brook Retreat, Keene, California, has taken over his duties as Medical Director and Superintendent of the Alexander County Tuberculosis Hospital, Cairo, Illinois

Drs. Alvan L. Barach and Chesmore Eastlake, Jr., New York City, and Dr. Maurice S. Segal, Boston, will participate in a symposium on inhalational therapy being presented under the auspices of the New York Academy of Medicine and the New York Association of Oxygen and Ambulance Services, Inc. The symposium will be presented at the Academy Building, New York City, December 5 to 10, inclusive

Dr. Evarts A. Graham, St. Louis, Missouri, has been honored by the Mississippi Valley Medical Society as its Honor Award Recipient for 1949. The award, consisting of a gold medal and a certificate, was presented at the annual meeting of the society in St. Louis on September 29

Dr. Edward W. Custer, South Bend, Indiana, has informed us that dedication ceremonies of the remodeled and enlarged Healthwin Hospital, of which he is Superintendent, were held on Saturday, September 18, and attended by more than 600 persons. The principal speaker was Dr. Ernest E. Irons of Chicago, President of the American Medical Assn

Interim Session, American Medical Association

The Interim Session of the American Medical Association will be held in Washington, D. C., December 6 to 9, inclusive. The General Chairman of this meeting is Dr. Oscar B. Hunter of Washington, D. C., who is the President of the Southern Medical Association. The meeting is primarily for general practitioners. An interesting program on diseases of the chest has been arranged. Dr. Jay Arthur Myers, Minneapolis, Minnesota, is Coordinator for the Committee on Diseases of the Chest, Dr. J. Winthrop Peabody, Washington, D. C., is Sub-Chairman of the Committee. The other members of the committee are Dr. John W. Trenis, Dr. Daniel L. Finucane, Dr. A. Barklie Coulter, Dr. Sol Katz, Dr. Frank Ashburn, and Dr. Edgar W. Davis, all of Washington, D. C.

The following program will be presented in the session on diseases of the chest

"Modern Treatment of Cough,"

Andrew L Banyai, M.D., F.C.C.P., Milwaukee, Wisconsin

"Pulmonary Infarction,"

Hugh H Hussey, M.D., Washington D C

"Silent Lesions of the Lung,"

Edwin R Levine, M.D., F.C.C.P., Chicago, Illinois

"Bronchiectasis and Lung Cysts,"

Martin J Sokoloff, M.D., F.C.C.P., Philadelphia, Pennsylvania

"Physiologic Therapy in Bronchial Asthma and Pulmonary Emphysema with Motion Pictures of Bronchial Asthma and Obstructive Dyspnea,"

Alvan L Barach, M.D., F.C.C.P., New York, New York

"Tuberculosis and the General Practitioner,"

Jay Arthur Myers, M.D., F.C.C.P., Minneapolis, Minnesota

"Chemotherapy in Tuberculosis Its Integration with other Procedures "

H McLeod Riggins, M.D., New York, New York

"History of BCG and Its Present Day Problems,"

Konrad Birkhaug, M.D., Albany, New York

"The Approach to Early Diagnosis and Surgical Treatment in Chest Disease,"

Norman Wilson, M.D., Boston, Massachusetts

"Comments on Mass X-Ray Surveys and Surveys of General Hospital Admissions for Pulmonary Tuberculosis,"

Robert J Anderson, M.D., F.C.C.P., Washington, D C

"Hematogenous Tuberculosis with Emphasis on the Value of Bone Marrow Study for Diagnosis,"

Sol Katz, M.D., Washington, D C

"Lipoid Pneumonia "

A O Hampton M.D., Theodore Winship, M.D., Edward B McCabe M.D. and Edgar W Davis, M.D., F.C.C.P., Washington, D C

"A Panel on the Diagnosis and Treatment of the Pneumonias,"

Harry F Dowling, M.D., Washington, D C, Moderator

Thomas McPherson Brown, M.D. and Mark H Lepper, M.D., Washington, D C

"The Pathogenesis, Diagnosis and Treatment of Asthma,"

Maurice S Segal, M.D., F.C.C.P., Boston, Massachusetts

"Pleurisy with Effusion, Spontaneous Pneumothorax and Other Diseases of the Pleura,"

Louis L Friedman, M.D., F.C.C.P., Birmingham, Alabama

Aerosol Therapy for Bronchopulmonary Disease,"

Maurice S Segal, M.D., F.C.C.P., Boston, Massachusetts

Trauma of the Lungs and Pleura "

J Maxwell Chamberlain, M.D., New York, New York

"Recent Advances in Fungus Diseases of the Lungs "

Harman E Bass M.D., F.C.C.P., New York, New York

"Medication and Practical Principles in the Management of Coughs "

A Worth Hobby, M.D., F.C.C.P., Atlanta Georgia

Sarcoidosis,"

Sol Katz M.D. Washington D C

Differential Diagnosis of Chest Pain,

Hugh H Hussey, M.D. Washington D C

A Panel on Pulmonary Diseases Due to Inhalation of Certain Organic and Inorganic Dusts with Comments on the Compensation Problems "

Anthony J Lanza M.D., New York New York Chairman

Edgar Mayer, M.D., F.C.C.P. New York New York and Oscar A

Sander M.D. F.C.C.P., Milwaukee, Wisconsin

Pulmonary Hemorrhage "

Ossler A Abbott M.D., F.C.C.P. Atlanta Georgia

The Surgical Management of Bronchiectasis "

Herbert C Mayer M.D. New York, New York

"The Surgical Treatment of Lung Abscess,"

Roy G Klepser, M D , F C C P , Washington, D C

"Bronchial Obstruction, Clinical and Bronchoscopic Observations,"

Paul H Holinger, M D , F C C P , Chicago, Illinois

"Clinical Aspects of Pulmonary and Mediastinal Neoplasms,"

Foster Murray, M D , F C C P , Brooklyn, New York

National Medical Association Creates Section on Diseases of the Chest

The first Annual Meeting of the newly-created "Section on Diseases of the Chest of the National Medical Association," was held in August at the Horace Rackham Educational Building in Detroit, Michigan on the occasion of the Association's 54th Annual Convention. The following program was presented at the Educational Building and at the Rest Haven Hospital

"The Etiology and Management of Hemoptysis,"

M R Hadley, M D , F C C P , Chief, Tuberculosis Clinic, McKeesport Hospital, McKeesport, Pennsylvania

"Newer Concepts of Streptomycin Therapy in Tuberculosis,"

W Roderick Brown, M D , F C C P , School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

"Indications for Surgery in the Treatment of Tuberculosis,"

Arthur G Falls, M D , F C C P , Associate Attending Surgeon, Provident Hospital, Chicago, Illinois

"Mass X-ray Surveys in New Jersey,"

J Earle Stuart, M D , F C C P , New Jersey State Health Department, Plainfield, New Jersey

"The Management of Tuberculosis Complicated by Diabetes,"

Clarence H Payne, M D , F C C P , Municipal Tuberculosis Sanitarium, Chicago, Illinois

"Artificial Pneumothorax,"

G Leonard Oxley, M D , Harrisburg Hospital, Harrisburg, Pennsylvania

"The Use of Para-Aminosalicylic Acid in the Treatment of Tuberculosis,"

R C L Markoe, M D , F C C P , Medical Director, Fairview Sanitarium, Detroit, Michigan

"Diagnostic Problems of Carcinoma of the Lung,"

J Edmond Bryant, M D , F C C P , Chief, Chest Division, Provident Hospital, Chicago, Illinois

"Symposium on Diseases of Chest,"

Thomas H Billingslea, M D

The following officers were elected for the ensuing year

W Roderick Brown, M D , F C C P , Chairman

J Edmond Bryant, M D , F C C P , Chairman-Elect

Arthur G Falls, M D , F C C P , Secretary

J Earle Stuart, M D , F C C P , Chairman, Program Committee

Among the recommendations approved was the suggestion of a demonstration X-Ray Chest Survey of the members of the National Medical Association at the 1950 Convention

Arthur G Falls, M D , F C C P , Secretary

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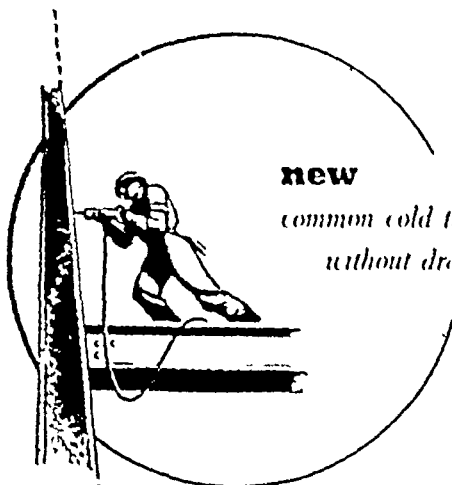
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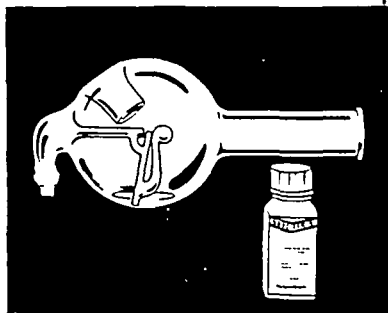
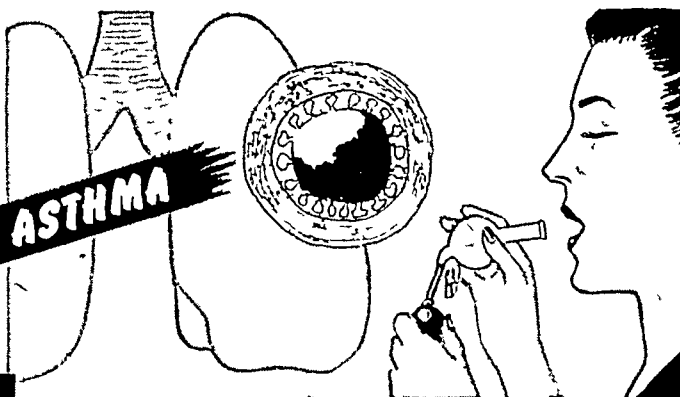
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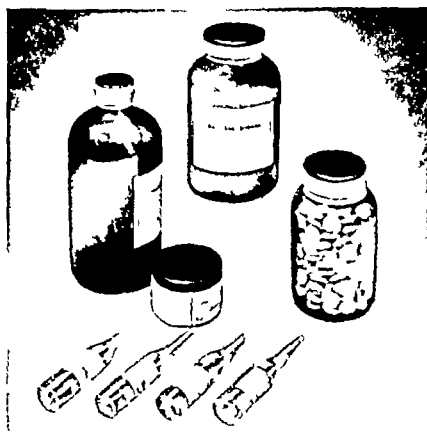
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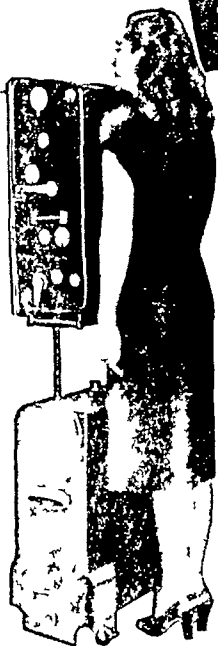
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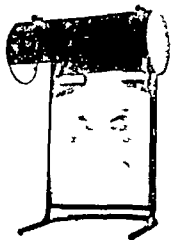
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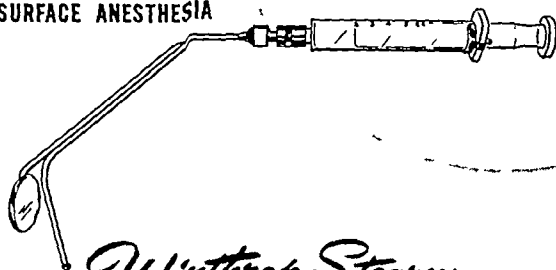
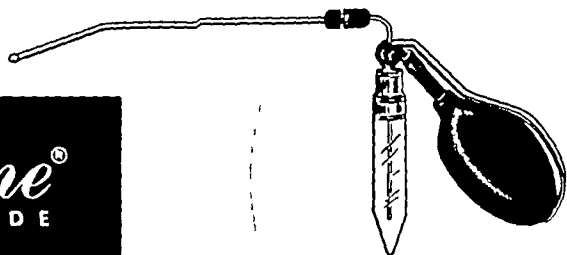


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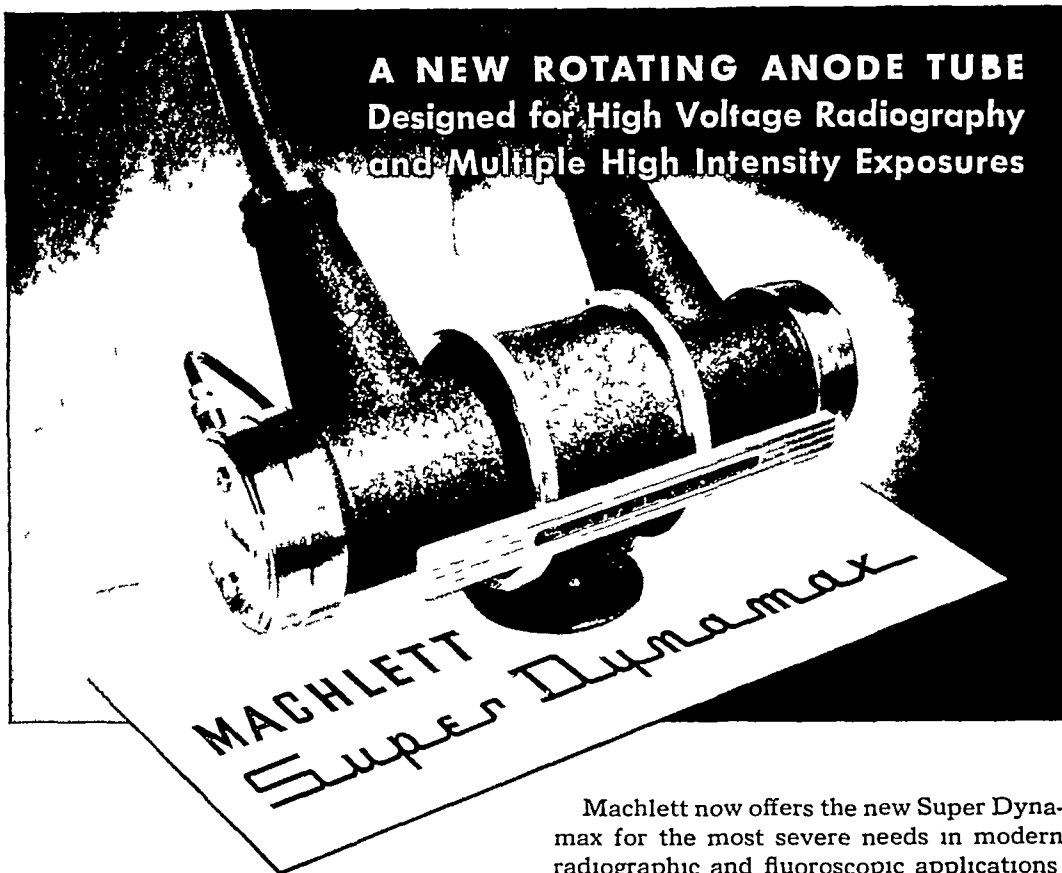
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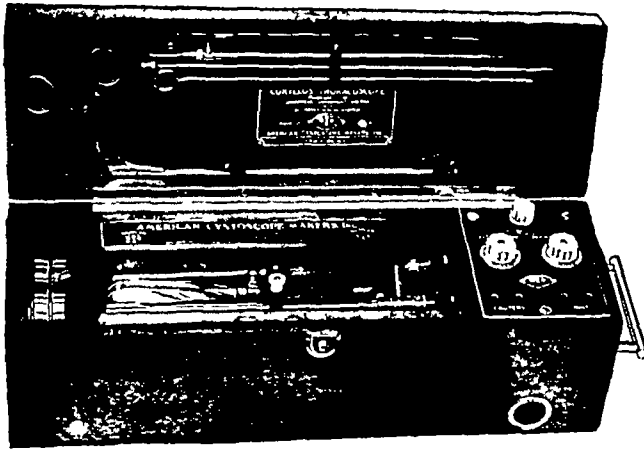
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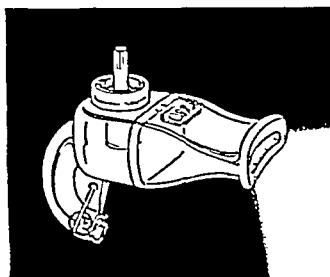
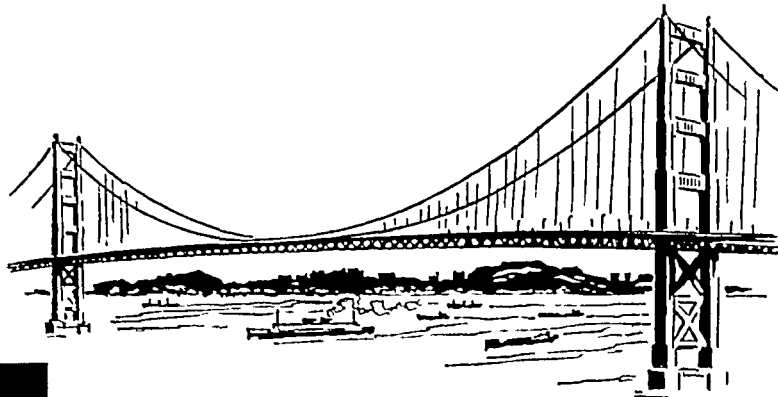
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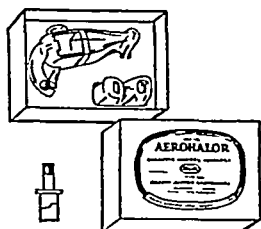


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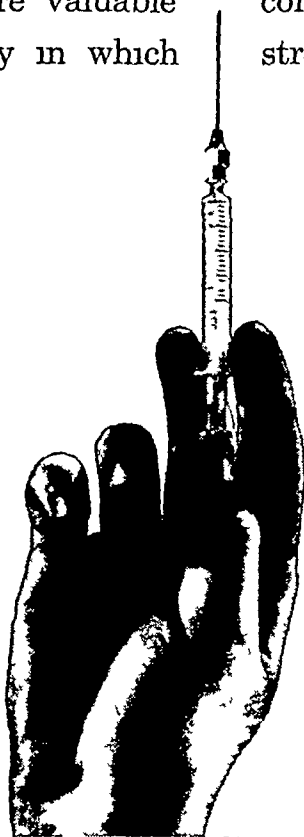
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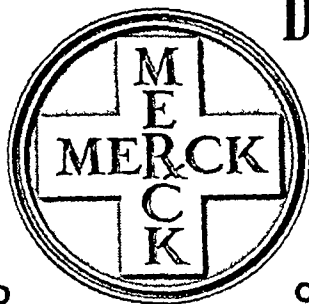
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DISEASES *of the* CHEST

VOLUME XVI

DECEMBER 1949

NUMBER 6

A Preliminary Report on the Use of Para-Amino Salicylic Acid in the Treatment of Pulmonary Tuberculosis

HENRY C SWEANY, M D, F C C P, GEORGE C TURNER, M D, F C C P,
MEYER LICHTENSTEIN, M D and SAMSON ENTIN, M D
Chicago, Illinois

In 1944 Lehmann,^{1,2} in Sweden, first used para-amino salicylic acid to inhibit the growth of tubercle bacilli in vitro. The drug's action on the tubercle bacillus was thought probably due to an effect on the oxidation-reduction mechanism in the metabolism of the microorganism. It was shown earlier by Bernheim³ that salicylic and benzoic acids increase the oxygen uptake on growing tubercle bacilli. The natural sequence was to find a chemical that would have the opposite effect. A large number of related compounds were studied, but the para-amino salicylic acid was found to be the most effective in suppressing the growth of tubercle bacilli. The peculiar feature is that only when the amino group is in the "para" position is there a reversal of oxygen uptake. It was later found by Sievers⁴ that the drug, conveniently designated as P A S, inhibited the growth of tubercle bacilli, but had no effect on a large number of other pathogenic bacteria. In this respect it differed from most of the new chemotherapeutic agents.

Lehmann's work on experimental tuberculosis in guinea pigs

*Presented at the 15th Annual Meeting of the American College of Chest Physicians, June 2-5, 1949, Atlantic City, New Jersey

From the City of Chicago Municipal Tuberculosis Sanitarium Clinical and Research Departments

This investigation was supported (in part) by a Research Grant from the Division of Research Grants and Fellowships of the National Institutes of Health, U S Public Health Service

Acknowledgment and appreciation is hereby accorded to Park, Davis & Company, Detroit, Michigan, for the generous supply of P A S used in these experiments

elicited some toxic reactions. The animals lost appetite and failed to grow. Paradoxically, he encountered only slight toxic effect in human beings, most of which was manifest as gastro-intestinal irritation.

The first clinical report by Lehmann was encouraging, and later joint reports by Vallentin and his associates⁵ throughout Sweden, as well as reports by Alin and Difs,⁶ Dempsey and Logg,⁷ Lemming,⁸ and others, have confirmed the fact that certain forms of tuberculosis appear to respond favorably to treatment with the drug P A S. has been found effective particularly to enteritis, skin sinuses, genito-urinary tuberculosis and in ulcers of the pharynx and tracheo-bronchial tree. Patients with meningitis improved in clinical symptoms, but no case has yet recovered on P A S treatment alone. Carstensen and Sjolín⁹ reported good results on secondary tuberculosis enteritis.

In this country, Youmans¹⁰ first produced a suppression of the disease in vitro and, contrary to Lehmann's findings, Feldman, Karlson and Hinshaw¹¹ and Youmans and his associates¹² observed little unfavorable effect of the drug on animals. Of much significance was the observation by the latter group that P A S inhibited the growth of six strains of human tubercle bacilli already resistant to streptomycin.

In pursuing the delay in streptomycin resistance of tubercle bacilli following P A S treatment, Karlson, Pfuetze, Carr, Feldman and Hinshaw¹³ reported that they were able to find only one streptomycin-resistant strain after three months treatment out of fourteen cases of tuberculosis treated on a combined regimen of P A S, streptomycin, and promin. Only three resistant strains were found after six months of treatment.

The Problems Involved

The problems confronting us in this study were to ascertain the extent of the toxicity of P A S on human beings, to determine its effect on clinical tuberculosis, to see if it decreased the development of resistance of tubercle bacilli to streptomycin when used with streptomycin, and to find out whether it produced a favorable result after streptomycin had failed, or when streptomycin was otherwise ineffective.

Methods

Preparation and Administration of the Drug At first the tablets of P A S were given alone, but later the acid was neutralized with 0.6 gm NaHCO₃ per gram of P A S. The salt then produced was given in a liquid preparation in a dosage of 3 grams four times daily, usually with food.

The Control Studies of Treated Patients Prior to treatment, the following laboratory examinations were made. Complete blood count and sedimentation rate, nonprotein nitrogen, total protein, and albumin-globulin ratio, urine analysis, and sensitivity of organisms to P A S and streptomycin. Blood levels of P A S were routinely taken on the tenth day of treatment. Urinalysis was repeated every two weeks, complete blood count, sedimentation rate, x-ray films of the chest, and sensitivity of organisms were repeated every thirty days. X-ray films of the chest were repeated every thirty days and following the end of therapy. Protein partition was performed every three months and at the end of treatment.

X-Ray Analysis Analysis of the x-ray changes was estimated by two unbiased observers,* who gave opinions on series of x-ray films of patients who had received P A S therapy, streptomycin therapy, placebo therapy, or only rest therapy. The observers had no knowledge of the kind of treatment the patients were receiving. They first evaluated a pre-treatment plate, then compared plates taken at 30 day intervals, employing classifications: Worse, stationary, slight improvement, moderate improvement, marked improvement.

Clinical Examinations The clinical condition of the patient was followed by personal interview and examination of each patient at two week intervals, at which time information was tabulated concerning cough, expectoration, weight, etc.

The results include work on groups of patients, most of whom have finished four months of therapy with the exception of the group investigated on fever alone. A few patients had six months' treatment.

Clinical Trial of P A S on Pulmonary Tuberculosis The number of cases treated so far, is too small to give anything but a general impression of the effectiveness of P A S against pulmonary tuberculosis. There was a definite and unmistakable improvement in over half of the cases. The cases treated were of two general types—the acute "exudative," or those with recent infiltrative lesions, and cases with chronic fibro-caseous and ulcerative lesions. Almost all cases treated were far advanced, many having a prognosis of zero at the time the treatment was begun. Six fairly representative case histories and x-ray reproductions will be given to illustrate the various aspects of the study.

Cases with Pneumonic and Infiltrative Lesions Of the acute infiltrative type there were eight cases. One died soon after the treatment was begun, and in another the drug was discontinued.

*Dr. Leroy Berard, Clinician, and Dr. Flora Brown, Roentgenologist

because of gastro-intestinal symptoms. Of the other six, one became worse, with a spread to the other side, one remained stationary, one was slightly improved, two moderately improved, and one was markedly improved. There was improvement in 50 per cent of all the cases in this group.

The first case history presented is that of the patient who showed no improvement and actually became worse for awhile. Later her condition became stationary.

Case 1 VD, No 61649 was a thirty-one-year-old negro housewife, married and with two children of ages thirteen years and sixteen months, respectively. The children were living and well. The patient's contact with tuberculosis was unknown.

Onset was insidious and first noted in September, 1948.

Past History was not significant.

Present Illness began with a non-productive cough in September, 1948. Soon after, the patient noticed a loss of appetite and weight. About two months later the patient began to run a fever and to have night-sweats. She lost twenty-three pounds in three months.

Physical Findings The patient was sixty-one inches tall and weighed eighty-nine pounds. Her average weight was one hundred pounds, her best weight one hundred and twelve pounds. The cough was productive of 125 cc of mucopurulent sputum daily, positive for tubercle bacilli. The x-ray examination revealed that the major portion of the right lung was occupied by a soft consolidation, most dense in the base. A cavity 3 cm in diameter was seen in the second interspace, apparently localized in the apex of the right lower lobe. It was thought also that a lesion might be developing in the left lung at the level of the first interspace close to the mediastinum. The diagnosis was pulmonary tuberculosis FAB.

PAS Treatment was begun January 17, 1949. The laboratory findings prior to treatment were as follows:

Blood Red blood corpuscles, 4,630,000, white blood cells, 10,350, hemoglobin, 78 per cent, red cell sedimentation rate (Cutler method), 22 mm in one-half hour.

Non-Protein Nitrogen 24 mg per cent.

Urine was negative for albumen and sugar and had a specific gravity of 1.011.

Sputum was positive for tubercle bacilli on concentration.

Progress Notes The patient did well clinically until March 31, 1949. She had gained six pounds, her temperature decreased, her cough was less, and expectoration had diminished from 60 to 30 cc daily. However, at that time it was noted that a new lesion had developed in the middle one-third of the left lung, extending outward from the left hilum. The x-ray film showed clearing of the exudative components of the right lung, but a cavity in the apex of the right lower lobe had increased in size. Although PAS was continued, the chest findings became more pronounced, rales appeared in the left lung, and the patient developed a severe cough, with increased expectoration to 100 cc daily.

At the present time (June, 1949) the cough has again diminished remarkably, and the chest findings in the left are minimal. There is now much clearing of the new lesion on the left and further clearing of the extensive lesion on the right.

The sputum was cultured on May 5, 1949, and found positive for tuber-

cle bacilli The bacilli were sensitive to less than 1 microgram of streptomycin Bacilli from a culture of February 16, 1949, were sensitive to less than 0.1 mg per cent P.A.S. The sputum culture was negative on concentration in June, 1949

The red blood count on June 1, 1949, was 4,320,000, white blood count, 11,100, hemoglobin, 69 per cent, sedimentation rate 25 mm

Case 2 FF, No 61615 was a thirty-six-year-old white male, married and having one healthy child six years old His occupation was that of bartender The contact is unknown

The Onset was insidious in November, 1948

Past History The patient suffered a dislocation of the right hip with an osteomyelitis in 1917 He had been a heavy drinker, consuming a fifth of a gallon of liquor daily in the year prior to admission

Present Illness The patient had had a morning "cigarette cough" with production of 5-6 cc of mucoid sputum daily for some years

Physical Findings The patient appeared chronically ill, symptoms were moderate There were exaggerated breath sounds, and moisture and dullness in the right apical region The sputum was positive The x-ray inspection disclosed soft exudative consolidation scattered throughout the upper half of the right lung with numerous small irregular cavities throughout At least one fairly large cavity was seen to fill the apex of the right lung There was no definite involvement seen in the left lung The liver was palpable The diagnosis was pulmonary tuberculosis FAB

P.A.S. Treatment was begun on January 3, 1949 The laboratory findings preceding treatment were as follows

Blood Red blood corpuscles, 3,990,000, white blood cells, 10,250, hemo-

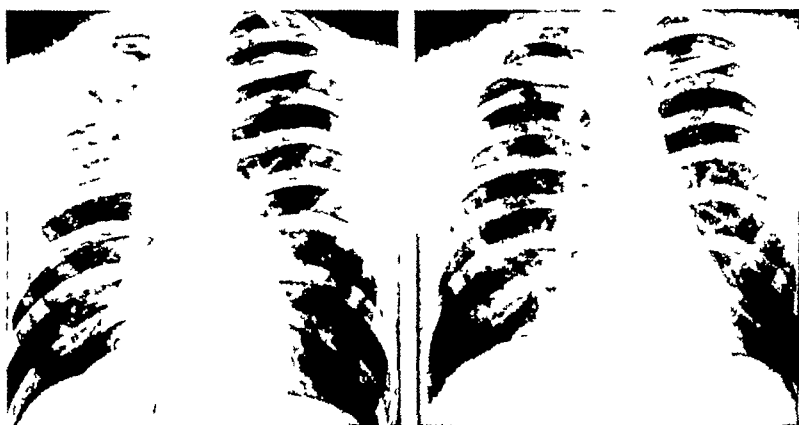


FIGURE 1

FIGURE 2

Fig 1 Roentgenogram of Case 2 (FF) taken November 23, 1948 before P.A.S. was given There was a mass of irregular infiltration in the whole right upper lobe There were many small irregular annular shadows throughout and one large one in the apex—*Fig 2* Another x-ray film taken of the same case May 28, 1949 nearly two months after the end of the treatment—much clearing of infiltration and all the annular shadows had disappeared from view Pneumothorax was instituted on the right on May 24 1949 While some of the clearing may be due to bed rest and change in habits, the change noted would practically never have happened on regular treatment in the same period of time



FIGURE 3

FIGURE 4

FIGURE 5

Fig 3 Roentgenogram of D W taken July 15, 1939, eight years before treatment, showing extensive bilateral fibro-ulcerative disease
Fig 4 Same case on May 27, 1948, twenty-three days before P A S treatment was begun after eight years of progressive disease Note the many early bilateral cavities —*Fig 5* Same case on August 9, 1948, fifty-eight days after P A S treatment was begun There was a marked shrinking of all the visible cavities with slight clearing of the infiltrative lesions

globin, 66 per cent, red cell sedimentation rate (Cutler's method), 25 mm in one-half hour

Non-Protein Nitrogen 34 mg per cent, fibrinogen, 0.74 gm per cent, globulin, 2.80 gm, A-G ratio, 1.49, total protein, 7.71 gm, serum bilirubin, within normal limits, cephalin flocculation, negative

Urine Specific gravity, 1.012, other findings negative

Progress Notes The patient showed marked clinical improvement, with a gain of 23¾ pounds in weight (June 1, 1949). The temperature became normal. There was no definite change in cough or expectoration, but his general condition was good. The x-ray film showed moderate improvement in the extensive disease in the right upper lobe (Figs 1 and 2).

The sputum remained positive on concentration. A culture done on May 9, 1949, was positive, and the bacilli were partially resistant to 1 mcg streptomycin. Bacilli from a culture of March 4, 1949, were sensitive to less than 0.1 mg per cent P.A.S. A right pneumothorax was initiated on May 24, 1949.

Shortly after this time, the red blood count was 4,810,000, white blood count, 12,100, hemoglobin, 85 per cent, sedimentation rate, 20 mm (19 per cent gain). The non-protein nitrogen was 31 mg per cent, fibrinogen, 0.57 gm per cent, albumen 4.38 gm, globulin, 2.27 gm, A-G ratio, 1.93, total protein, 7.22 gm. The urine was normal.

This second case made a marked improvement.

Of the chronic fibro-caseous and ulcerative cases, there were three categories treated. The first included seven cases treated for 120 days or more. One patient left before the treatment was finished, and one is still under treatment. Of the five remaining cases, one was worse, one was stationary, one was slightly improved, one moderately improved, and one markedly improved. Of the completed cases, 60 per cent improved.

In Case 3 there was marked improvement, but resistance of the bacillus to P.A.S. developed with a relapse of the patient's condition.

Case 3 D.W., No 48647, was a fifty-one-year-old white female, single, and an office worker.

The Onset was catarrhal in July, 1939.

Past History The patient has been under the care of a physician for a multitude of ailments (nose trouble, arthritis, tuberculosis, etc.), from July, 1939, until 1947, when she began to cough and raise sputum.

Physical Findings X-ray inspection revealed infiltration of both upper lung fields. The diagnosis was pulmonary tuberculosis, F.A.B. Routine rest treatment was recommended.

Interval Note After some time, multiple thin-walled cavities appeared in both lungs. For at least two years prior to the institution of P.A.S., there had been a daily rise of temperature to 101.4 degrees F. The sputum was consistently positive. The patient has had vague abdominal distress, characterized by nausea, particularly when taking fruit juices. (An x-ray work-up, however, of the G.I. tract and gallbladder was negative). Over the last two years her weight has varied from 94 to 100 pounds.

P.A.S. Treatment was begun June 19, 1948, given 10 gms daily in four divided doses. The laboratory findings before the beginning of P.A.S. therapy were as follows:



FIGURE 6

FIGURE 7

FIGURE 8

Fig 6 Same case (D W) 123 days after P A S treatment, with continued shrinking of cavities and clearing of infiltrative lesions —
 Fig 7 Same case on January 22, 1949, at the time P A S treatment was stopped The bacilli on February 8, 1949, were resistant to 100
 mgs per cent P A S The clinical condition, the x-ray films (enlarging cavities) laboratory findings show deterioration of the patient's
 condition —Fig 8 Same case after retreatment with P A S , but to practically no avail

Blood Red blood corpuscles, 4,040,000, white blood cells, 8,600, hemoglobin, 66 per cent, red cell sedimentation rate (Cutler method), 22 mm in one-half hour. Bacilli from a culture of September 12, 1948, were sensitive to 0.39 mgs per cent P A S.

Urine The laboratory findings were negative.

The x-ray film showed bilateral, far-advanced pulmonary tuberculosis, with multiple cavitations.

Progress Notes Three days after the beginning of treatment, the temperature dropped to normal, with a single rise to 101 degrees F and an occasional rise to 99 degrees F. By December 31, 1948, the patient had gained four pounds, her G I symptoms had subsided, and she felt better and appeared clinically improved, though there was very little change on physical examination. On x-ray inspection (November 19, 1948), a remarkable decrease in the size of the cavities was noted.

On January 17, 1949, the patient showed considerable improvement in symptomatology. The x-ray film revealed marked clearing and remarkable diminution in the size of the cavities. P A S was discontinued on January 24, 1949.

The sputum culture of February 8, 1949, was positive, and the bacilli were resistant to approximately 100 mg per cent of P A S. All strains recovered were sensitive to less than 1 mcgm of streptomycin.

Her clinical condition again became progressively worse, she began running a low-grade fever, and the cavities increased in size. Her sputum had increased again from about 100 cc to nearly 300 cc daily.

A second course of P A S was started on April 4, 1949. The patient's general condition at this time is poor, she has been having slight hemorrhages for the past few weeks. The temperature rises to 99.4 degrees F, and there are probable extensive bronchial changes now present. The x-ray films do not reveal any essential changes since the beginning of the second course of P A S.

On June 1, 1949, the red blood count was 4,120,000, white blood cells, 6,500, hemoglobin, 70 per cent, sedimentation rate, 25 mm.

The second group consisted of thirteen cases treated with the drug. They were matched as closely as possible with thirteen similar cases, who were given a placebo instead of the drug. We were obviously not harming any of these control cases because most of them had a grave prognosis at the time of selection, and there was no other treatment indicated than bed rest.

Of the treated cases, only eight have finished ninety days of treatment. Of these, three have shown no improvement, three have shown slight improvement, while two have shown moderate improvement. The improved cases represent 62.5 per cent of those treated for ninety days.

The five remaining cases have completed sixty days, two are stationary, two slightly improved, and one moderately improved. The improved cases represent 60 per cent of the group.

Of the controls, six have had ninety days of treatment, two of these have become worse, and four others have not improved.

Of all the cases treated with P A S alone, there was a rather uniform improvement in fifty to sixty per cent of the acute and



FIGURE 9

FIGURE 10

FIGURE 11

Fig 9 Roentgenogram of Case 4 (V S) taken on October 2, 1947, 28 days before streptomycin treatment was given (1 gram daily for 46 days and then 0.5 gms daily for 74 days) —*Fig 10* Same case on February 11, 1948. After 113 days of streptomycin treatment, with marked clearing of the infiltrative lesions —*Fig 11* Same case on July 1, 1948, over four months after streptomycin was stopped, and 51 days before P A S was begun. Note the many cavities and new infiltrations.

chronic cases selected for treatment. Some of the cases have shown a remarkable improvement, too great to ascribe to anything else but the drug, especially since the control cases have shown no corresponding improvement. It appears to us, however, that the improvement is perhaps a trifle less and somewhat slower than we have observed in corresponding cases treated with streptomycin, but there is the possibility, rare in streptomycin-treated cases, of continuing the treatment for long intervals of time and thus achieving a result approaching, or perhaps exceeding, that obtained with streptomycin.

The Effect of P A S on Patients Failing to Respond to Streptomycin or Relapsing After a Temporary Improvement on Streptomycin

Fifteen cases are included in this group, but only nine are completed to date. Of the nine cases completed, two were worse, one was stationary, two slightly improved, and four markedly improved. Therefore, there were 55.6 per cent improved with 44.4 per cent markedly improved. One case (5), showing marked improvement, was given a pneumoperitoneum. It appears to us that this type of case offers a definite reason for optimism in the future use of P A S. In a few cases, there was an unequivocal favorable result where practically a zero prognosis had existed.

Case 4 V S, No 60014, was a 22-year-old white female, an office worker. The onset of the disease was catarrhal in June, 1947. The past history is not significant.

Present Illness. In June, 1947, the patient developed marked fatigue, cough and fever. An x-ray film taken in July, 1947, showed pulmonary tuberculosis. The patient spent one week in the Fresh Air Hospital, she was sent home and remained in bed there until admission to the Municipal Tuberculosis Sanitarium on October 1, 1947. There had been a twenty-five-pound weight loss in three months.

Physical Findings. The patient was 65½ inches in height, weighing 114½ pounds (her best weight had been 138 pounds). Her cough was moderate. She expectorated about 90 cc of thin, whitish-yellow sputum daily. The diagnosis was bilateral pulmonary tuberculosis. F A B.

Interval Note. The patient was put on bed rest, but there was no improvement. Her temperature rose to 102.0 degrees F.

Streptomycin Treatment. The patient was given 1 gm daily for forty-six days, then 0.5 gm daily for 74 days (from October 30, 1947, until February 28, 1948). She had shown remarkable clinical and x-ray improvement at the conclusion of the streptomycin course. She had become afebrile, gained thirteen pounds, and was asymptomatic. The streptomycin sensitivity test from a culture revealed that the bacilli were completely resistant to 100 micrograms on April 10, 1948, March 29, 1949, and May 4, 1949.

Interval Note. The clinical improvement was maintained for four months after termination of the streptomycin treatment, when symptoms began to reappear. The cough increased, and expectoration increased to about 120 cc. There was a daily elevation of temperature to



FIGURE 12

FIGURE 13

FIGURE 14

Fig 12 Same case (V S) on November 27, 1948, 110 days after P A S treatment with clearing and disappearance from view of most of the cavities—*Fig 13* Same case on December 24, 1948, about a month later, with more clearing—*Fig 14* Same case on April 30, 1949, 68 days after P A S was stopped, with marked clearing and a corresponding improvement in clinical condition, including a 23-lb gain in weight

99.0 degrees F The appetite became poor, and there was a weight loss of fourteen pounds in two months The x-ray film showed extensive involvement of both lungs with fibro-caseous and ulcerative lesions, multiple cavities were seen throughout the upper two-thirds of both lungs The disease had made a gradual progression since the completion of streptomycin treatment

PAS Treatment was begun on August 21, 1948, as 12 grams daily in four divided doses The laboratory findings before the beginning of treatment were as follows

Blood Red blood corpuscles, 4,380,000, white blood cells, 13,500, hemoglobin, 65 per cent, red cell sedimentation rate (Cutler method) 24 mm in one-half hour

Urine Specific gravity, 1.015, albumen, 1 gram per litre, sugar, negative

Progress Notes By December 31, 1948, the temperature had returned to normal except for two elevations to 99.0 degrees F The cough and expectoration had decreased The sputum culture was positive for tubercle bacilli in September, but negative in November There was a weight gain of seven pounds The patient felt better and appeared clinically improved There were no significant changes on the x-ray

The red blood cell count at this time was 4,300,000, the white blood cell count was 9,000, the hemoglobin was 80 per cent, and the sedimentation rate was 15 mm in one-half hour

On June 10, 1949, the patient, still showing clinical improvement, weighed 137½ pounds (a gain of 23 pounds since the beginning of therapy) PAS treatment was stopped on February 21, 1949 At that time there was a diminution or disappearance of some of the cavities, otherwise the findings were the same as before In general there was considerable x-ray improvement The sputum was positive on direct smear and on culture since January 10, 1949 On May 4, 1949, the red blood count was 4,400,000, white blood cells, 9,600 hemoglobin, 79 per cent, sedimentation rate, 14 mm The culture was resistant to 100 mcgms of streptomycin

Case 5 LN, No 59577, was a twenty-six-year-old white female, married She did factory work until May, 1947

The Onset was insidious early in 1946

Past History The patient had frequent colds There were three episodes of "flu," the last one year ago

Present Illness The first sign of trouble was a "cigarette cough" followed by irritability, fatigue and night sweats

Physical Findings There was an expectoration of 5-10 cc of clear sputum daily The patient complained of a dull pressure over the left chest with dyspnea on moderate exertion Her temperature was 99-100 degrees F There had been a 22-pound loss in weight over the past 1½ years, from 116 pounds to 89 pounds The height was 63½ inches The pulse was 96 and the blood pressure 96/58 The x-ray findings revealed several cavities and soft infiltration involving the upper two-thirds of the left lung and a small patch of infiltration in the right mid-lung field The diagnosis was pulmonary tuberculosis, FAB

Interval Notes On June 24, 1947, a pneumothorax was performed on the left side, an intrapleural pneumolysis was done on July 24, 1947, following which the patient developed fluid Her temperature rose to 104.0 degrees F, but later subsided to 99.2 degrees F, the expectoration

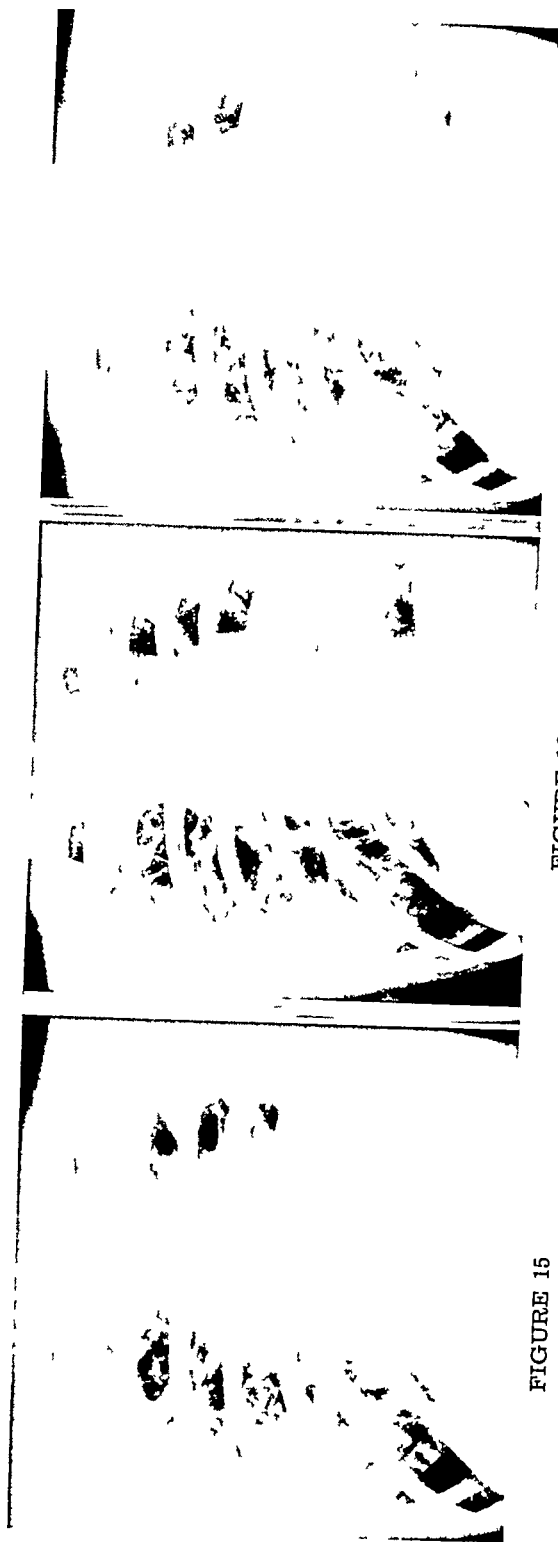


FIGURE 15

FIGURE 16

FIGURE 17

Fig 15 Case 5 (L N) was a roentgenogram taken January 21, 1948, one month before streptomycin treatment was begun. There were many scattered nodules throughout both lungs, a few small cavities in the right lung, and a left empyema following an unsuccessful pneumothorax.—*Fig 16* Same case taken on May 21, 1948, 81 days after 0.5 gram daily dosage of streptomycin treatment was begun. There was much clearing through both lung fields.—*Fig 17* Same case taken July 22, 1948, 29 days after the streptomycin treatment was stopped, and 39 days before P A S was begun. Note enlarging of cavities on right and beginning reexpansion of the left lung.

ceased, and the patient gained 11 pounds. The x-ray inspection, however, showed progression of the disease on the right side.

Streptomycin Treatment was begun on February 28, 1948, and continued until June 2, 1948 (94 days) in 0.5 gm daily doses, given in two injections. At the conclusion of the streptomycin therapy, the x-ray film showed considerable clearing. The temperature was normal throughout the course. The appetite improved somewhat, but the weight remained constant. The general clinical condition seemed only slightly, if at all, improved.

Interval Note The general condition remained unchanged, but after one month, the x-ray film revealed progression of the disease on the right side.

The red blood cell count on August 26, 1948, was 4,540,000, white blood cell, 7,500, hemoglobin, 70 per cent, sedimentation rate, 25 mm in one-half hour.

PAS Treatment was initiated on August 30, 1948, and given as 12 gm amounts daily, divided into four doses.

Progress Notes On December 31, 1948, the sputum was negative on culture, the temperature was normal, the expectoration was 5-10 cc daily. There was no gain in weight. The patient stated that she felt better, and she appeared clinically improved. The x-ray film showed an increased fluid, but with a noticeable improvement in the tuberculosis lesions.

A pneumoperitoneum was instituted on April 1, 1949.

By June 10, 1949, the patient had gained five pounds, weighing 101 pounds at the end of treatment. The cough and expectoration were about the same as before treatment. The x-ray inspection revealed considerable clearing in the disease of the right lung, with closure of several cavities previously noted, and diminution in the size of the others. The left empyema showed a slight decrease in size.

The sputum has been negative on concentration since June 3, 1948, and negative on culture since August 12, 1948.

On May 4, 1949, the red blood cell count was 5,090,000, white blood cells, 10,000, and hemoglobin 83 per cent.

Combined PAS and Streptomycin

Finally a group of cases were treated with combined streptomycin and PAS. This was done for several reasons. First, we wanted to see if we could get the additive results of the combined drugs, second, we desired to see if there was an increase over the simple summation of the results of two drugs as indicated by the experimental work of Vennesland, Ebert and Bloch,¹⁴ and finally, we wanted to test the principle expressed by Karlson¹³ and his associates as to the delay in the development of resistance of the bacilli to streptomycin as a result of treatment with PAS.

In this group there were nine cases, two of which had received previous courses of streptomycin, and two of which have not yet finished treatment. The two who had received previous treatment both improved, one slightly and one moderately. Of five cases completed, all showed improvement. One was slightly improved, two were moderately improved, and two were markedly improved.



FIGURE 18

FIGURE 19

FIGURE 20

Fig 18 Same case (L N) taken February 7, 1949, 38 days after P A S treatment was completed. At this time more clearing was present, the cavities were lost to view, and the left lung was reexpanding — Fig 19 Same case on April 5, 1949, 57 days later after the introduction of pneumoperitoneum. Slightly more reexpansion on the left, but little other change — Fig 20 Same case on June 3, 1949, and showing slightly more clearing with a marked shrinking of the thin-walled annular shadow on the right. The lower annular shadow on the right has been lost to view.

Case 6 H W, No 61721, was a twenty-three-year-old white female waitress, divorced, with no children The contact was unknown

The Onset of the disease was with an upper respiratory infection in June, 1948

The Past History is not significant The patient suffered a G U or ovarian (?) disorder in 1948

Present Illness In June, 1948, the patient developed an upper respiratory infection accompanied by productive cough This cleared in about ten days, but returned in September, accompanied by left chest pain and exertional dyspnea The cough became increasingly severe, and night sweats began in November

Physical Findings The patient was 64 inches tall, weighing 121 pounds Her pulse was 76 4 and regular, blood pressure was 110/40 She had a cough with expectoration of 1 cc yellowish-white sputum, which was positive on culture She complained of pain in the left lower chest on respiration The x-ray film disclosed scattered exudative disease throughout the entire right upper lobe and in the upper two-thirds of the left lung At least three large cavities (measuring 3 cm in diameter) and numerous smaller ones were seen Diagnosis, pulmonary tuberculosis, FAB An x-ray film of the colon was suggestive of a disease process at ileocecal junction

P A S Treatment was begun on February 7, 1949 The blood count preceding treatment was as follows Red blood corpuscles, 4,420,000, white blood cells, 9,300, hemoglobin, 74 per cent, sedimentation rate (Cutler method), 18 mm in one-half hour

Progress Notes The patient gained eight pounds, her cough and expectoration decreased, and she felt better and stronger Her temperature has remained normal The x-ray inspection showed marked improvement with resolution of the exudative components and closure of the many cavities On the latest film (May 13, 1949) no definite cavities were



FIGURE 21

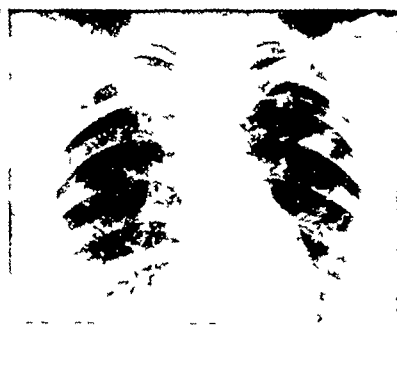


FIGURE 22

Fig 21 Roentgenogram of Case 6 (H W) taken on January 19, 1947 19 days before combined treatment of streptomycin and P A S was begun The streptomycin was given 45 days and the P A S was continued—*Fig 22* Same case 95 days after treatment was begun showing much clearing with a disappearance from view of large cavity in left upper lung field The clinical condition was greatly improved and the sputum was negative on concentration and culture since March 10, 1949

visible Improvement is still taking place The sputum has been negative on concentration and on culture since March 10, 1949 On June 1, 1949, the red blood cell count was 4,610,000, white blood cells, 4,900, hemoglobin, 82 per cent, sedimentation rate, 3 mm in one-half hour

Although the cases are too few for statistical purposes, the results do indicate that there is a definite advantage—certainly no disadvantage—in a combined regimen

The question of a delayed bacillary resistance to streptomycin was not established because the material was insufficient Of the two cases formerly treated with streptomycin, one was resistant to 10 mcgms, the other to 100 mcgms The latter case turned sputum negative after three months of combined treatment

Of the remaining seven cases, three turned negative before sixty days with none having a resistance to any more than 1 mcgm streptomycin Three others became slightly resistant to 10 mcgms within five weeks' time, but thus far there has been practically no increase over that figure The last case revealed partial resistance to 15 mcgms two months after treatment, but turned negative and remained negative for six months After nine months the sputum turned positive again, and the bacilli had a resistance to 10 mcgms *

Forty of the cases treated one way or another with P A S are assembled in Table I There is some improvement in twenty-eight (70 per cent) of the forty cases deemed worthy of reporting at this time

*We are grateful to Dr Guy P Youmans for the reports on sensitivity of the tubercle bacilli to streptomycin and P A S

TABLE I
A Summary of 40 Cases Treated with P A S

	Worse	Stationary	Slight Imp	Mod Imp	Marked Imp	Total
Acute 'Exudative'	1	1	1	2	1	6
Ch Fibro-Cas and Ulc, 120 days	1	1	1	1	1	5
Ditto, 90 days		3	3	2		8
Ditto, 60 days		2	2	1		5
Streptomycin Failures	2	1	2		4	9
Comb Streptomycin and P A S			2	3	2	7
TOTAL	4	8	11	9	8	40

*A Comparison of the Roentgenograms of all P A S Treated Cases,
Placebo Treated Controls, and a Group of Streptomycin
Treated Cases*

Adopting the method used by the Government Services to evaluate streptomycin treatment, we assembled all the roentgenograms of thirty-six completely treated P A S cases, with twenty regularly treated streptomycin cases treated simultaneously and twenty fibro-ulcerative control cases who had been treated with a placebo or only with routine rest. Two of our colleagues (Berard and Brown) appraised each case according to the plan described earlier. Table II shows the result of this analysis. There was only a slight improvement in some of the placebo treated cases, such as would be expected under regular sanitarium treatment. The P A S and streptomycin treated cases, on the other hand, revealed a gain that can only be interpreted on the basis of an intervention of something besides routine treatment. The results in the two (P A S and streptomycin treated cases) were similar with little to choose between them. There was improvement in 75 per cent of the streptomycin treated cases and 70 per cent of the P A S treated cases.

TABLE II
A Comparison of the Results of P A S and Streptomycin
Treated Cases with Controls

X-Ray Results 120 Days Rx	Placebo Rx (Chr Fibroids) 20 pts	P A S (Chr Fibroids) 16 pts	P A S 20 pts	Streptomycin 20 pts
Worse	15%	15%	10%	15%
Stationary	55%	33%	20%	10%
Slight Imp	20%	33%	25%	15%
Moderate Imp	5%	15%	10%	25%
Marked Imp	5%	0%	35%	35%

The chronic fibroid group treated with P A S did not fare so well, but still 48 per cent of this usually hopeless group of 16 cases showed temporary improvement. It should be borne in mind that the possibilities of rapid change in these cases rest only upon the clearing of peripheral infiltrates, some of which are not extensive and, therefore, do not register on the x-ray. The other changes consist of a slow removal of caseous foci, which change will probably not be fully revealed in the few months of observation.

The last change is that in the shape and size of the cavities and their walls. These changes are sometimes striking and consist of a shrinking of the cavities, a buckling and a thinning of the walls, sometimes to fine lines, or even to complete invisibility.

General Results

Toxic Effects of P A S One of the first problems to solve in any chemotherapeutic study is to note the possible drug toxicity in the therapeutic range, and the extent and nature of such toxicity.

P A S appears, up to the present, to be relatively free from permanent toxic action. Nearly all patients experience a mild to severe sensation of nausea only during the first few days of treatment. Practically all the toxicity results from the drug's irritating action on the gastro-intestinal mucosa, resulting in nausea. Most patients were helped by the addition of aluminum hydroxide preparations. On rare occasions vomiting and diarrhea resulted, which could be controlled by removal of the drug or by administering belladonna or opium mixtures. Sometimes the toxic action was lessened and stopped by temporary reduction of the dosage. After a few days or weeks in such cases there appeared to be a development of tolerance so that the patient could continue the treatment through the required course. The drug should be given with the stomach filled if possible. Lehmann has recommended the use of "enteric" coated granules to prevent the action of the acid on the gastric mucosa. In addition, he contends that it facilitates a more uniform absorption. In our work we found very early that the toxic effect was reduced by giving the drug as an alkaline salt, although Lehmann contends that in the salt form, the drug is too quickly absorbed and eliminated. In only one case has treatment been discontinued entirely on account of gastro-intestinal symptoms.

In only one case was there an aggravation of an albuminuria already present, requiring discontinuation of treatment. A few patients developed skin reactions to varying degrees, but only one had to be taken off the drug on that account. No blood dyscrasias were found.

Whether any late effects will appear remains to be seen, but at the present time there do not seem to be any toxic effects that leave permanent damage, and very rarely is it necessary to discontinue treatment because of the temporary reactions.

Effect on Cough and Expectoration Diminished cough was noted by 50 per cent of the patients on P A S. In the control group on placebo medication, improvement in cough occurred in 15 per cent.

Diminished expectoration was noted by most of the patients in whom cough improved

Weight In the group on placebo therapy, less than half showed a slight gain in weight Of the patients on P A S, 70 per cent showed gains in weight, a few as much as twenty pounds or more during the period of observation

Effect on Fever Since many of the patients treated with P A S were afebrile, the effect of P A S on fever was studied in a group of twenty-four patients, who were seriously ill and failing Alternate patients were given P A S, the others, the placebo preparation At the end of three weeks, medication was stopped, and the effect evaluated one week later Six of the twelve patients receiving P A S showed a significant drop in fever In two of them the fever rose promptly upon discontinuance of the drug In the placebo group only two patients showed a decline in fever

X-Ray Changes We have considered the x-ray findings to be of the greatest interest and value in determining the effectiveness of this drug The most marked improvements among the P A S treated patients occurred in those with exudative lesions and those with tension cavities Considerable clearing and great diminution in the size of such cavities was commonly noted Among the chronic fibro-ulcerative cases improvement, if any, consisted of slight clearing of part of the lesions and slight diminution in the size of the cavities No *great* difference could be seen between the group treated with P A S and streptomycin and the group treated with streptomycin alone In general, the cases manifesting a favorable response to P A S showed the most marked improvement at the end of the four month period of treatment

Changes in Laboratory Findings

Conversion of Sputum Sputum studies have been made, but have not been followed long enough after the end of treatment to give any significant results There have been a few conversions of far advanced cases

Blood Levels Routine blood levels were always taken on the tenth day at 1 00 p m after treatment was begun A 24-hour blood level curve was studied in a number of other patients The curves were found to vary considerably in patients At one and two hours after each dose, the blood levels were between 1 0 mg per cent and 17 0 mg per cent, averaging 2 83 mg per cent The level seems to rise during the afternoon and to fall off in the evening There were only 1-3 mgs of the drug in the blood stream at 2 00 a m, six hours after the last daily dose, and practically

none by morning The complete data will be given in a subsequent report

Hemoglobin With one exception (Case 2) no significant effect was noted on hemoglobin after four months of P A S therapy or combined therapy in the patients studied Patients who showed definite improvement in sedimentation rate often showed no change in hemoglobin The large majority of patients, however, had no severe anemia before therapy

Sedimentation Rates Of patients on placebo therapy followed for four months, 15 per cent improved (Cutler method, 5 mm or more improvement in 30 min reading), 85 per cent were unimproved Of patients treated with P A S alone, 40 per cent showed improvement, with 60 per cent showing no improvement On combined therapy, 85.7 per cent showed improvement in the sedimentation rate The sedimentation rate was not influenced by the blood level of P A S

Resistance to P A S There were only three cases whose bacilli developed resistance to P A S—one to 5, another to 25 mgs, and another to 100 mgs Two were on long time treatment, and both have shown initial improvement with a later stationary or failing status The x-ray film on D W (Figs 3-8), show the deterioration of the pulmonary lesions corresponding approximately to the development of resistance Another patient had a similar improvement followed by a deterioration and finally death The third case was a placebo control at first, but was transferred to P A S therapy After less than a month a resistance to 100 mgs per cent of P A S developed If these three cases are any indication, it would seem that about 10 per cent of the bacilli of cases on P A S treatment will develop a significant resistance to the drug

Discussion

The results of these rather limited experiments permit us to make some deductions regarding the effect of P A S on pulmonary tuberculosis Up to the present, we are able to state that P A S exerts a decided favorable effect on some acute infiltrative lesions The x-ray findings, the clinical effects, and laboratory changes noted were fairly comparable to the results observed in streptomycin treated cases, but were not always as clear-cut and did not appear as soon as observed in streptomycin treated cases

In addition to the clearing of "exudative" disease, the drug appears to be of value to patients who have tension cavities Many cavities shrink, and some become lost to view after P A S treatment

In chronic fibro-ulcerative tuberculosis, there is the same erratic effect on some cavernous types with and without infiltration as

are observed in similar cases treated with streptomycin. The one big difference is that germ resistance is not of great significance for P A S. A more prolonged study is mandatory in this type of case since the drug appears to be practically harmless, produces clinical improvement, and lessens cough and expectoration in many patients of this type.

A second course of P A S therapy is being started in some of the patients who have finished a first course with apparent benefit, but whose disease was beginning to relapse. P A S may be used simultaneously or alternately with streptomycin, either one following the other as the circumstances warrant. Likewise, surgery may be used at the appropriate time. Case 5 (L N) is a good example where pneumoperitoneum was used successfully. Case 2 was given a pneumothorax after treatment.

In the matter of delaying resistance to streptomycin in combined treatment, there is some indication that resistance to streptomycin is slightly delayed, but our series is too small to be significant.

Finally, the favorable results on about half the cases failing to respond to streptomycin treatment or recurring after a temporary improvement, without any other factor, will probably insure P A S a permanent role in the treatment of pulmonary tuberculosis. The drug lends itself to prolonged courses of treatment, which may produce even better results than have already been reported.

CONCLUSION

P A S therapy was of considerable benefit when used on patients having pulmonary tuberculosis with exudative disease and tension cavities. It appears to have a definite effect on a few cases of chronic fibro-ulcerative tuberculosis, although the majority were not benefited. When used after streptomycin has failed, it improved nearly 50 per cent of the cases treated.

The drug does not appear to produce any marked resistance in tubercle bacilli. It does not seem to possess any permanent toxic effect when properly administered. For these various reasons, therefore, P A S appears to have a definite field of usefulness in the treatment of pulmonary tuberculosis.

CONCLUSION

La terapia con el P A S hizo mucho provecho cuando se le empleó en tuberculosos pulmonares con lesiones exudativas y cavidades de tensión. Parece tener un efecto bien definido en unos pocos casos de tuberculosis fibro-ulcerativa crónica, aunque en la mayoría no hizo provecho. Cuando se le empleó en casos en

los que habia fallado la estreptomycin, mejoraron casi el 50 por ciento de los casos tratados

La droga no parece producir decidida resistencia en los bacilos de Koch Tampoco parece tener ningun efecto tóxico permanente cuando se la administra apropiadamente Por estas varias razones se considera que el P A S parece tener un lugar bien definido en el tratamiento de la tuberculosis pulmonar

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D I S C U S S I O N

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We have treated 27 patients at Devitt's Camp with P A S for a period of from one to four months, and all patients are still under treatment. They fall into the following groups: Acute exudative, 1, Chronic fibroid, 5, Previously treated with streptomycin, 15, Silico-tuberculosis, 3, Far advanced extremely ill, 1, Combined P A S and streptomycin, 1, Tuberculous enteritis complicating pulmonary tuberculosis, 1.

Dosage was maintained at 15 grams daily in six divided oral doses at three hour intervals from 7 a m to 10 p m. Symptoms attributed to the drug were nausea, gas, diarrhea of varying degree, and these were controlled by Kaopectate or Kaomagma.

It is too early to evaluate treatment, but our results so far seem to parallel those of Dr. Sweeney's in his excellent preliminary report. Our best results were in the exudative lesions and in those patients who had ceased to improve under streptomycin or who had relapse following streptomycin.

X-ray improvement follows clinical improvement, but usually proceeds more slowly than with streptomycin. The improvement continues, however, at a steady and encouraging pace. Cavities show an encouraging decrease in size and some, including those of the tension type, have apparently closed. The case of tuberculous enteritis showed a remission of symptoms, after a recurrence during previous streptomycin.

I shall present three cases to illustrate reduction in cavities.

Case 1 I K, white, female, age 63. No improvement on bed rest only for seven months, with exudative disease left lung, severe cough, recurrent hemoptyses. P A S for three months with marked clinical improvement, and clearing on x-ray with disappearance of small cavities.

Case 2 D S, white, female, age 41. Long history of bilateral disease. Recent acute flare-up left lung with consolidation and ballooning of cavity following termination of streptomycin treatment. Marked clinical improvement after one month under P A S and definite x-ray clearing and reduction in size of cavity.

Case 3 H K, white, female, age 32. Appearance of tension type cavity in left lower lobe after clearing of exudative disease under streptomycin. The cavity was no longer visible after two weeks of P A S and treatment with the drug was continued, combined with pneumoperitoneum and left phrenic crush. Sputum negative on direct smear.

It seems logical to use P A S as a continuation treatment after streptomycin and to combine it with collapse therapy. One can

thus avoid or postpone development of resistant strains and can enhance the value of collapse therapy. One can also expect to use P A S as a preliminary to thoracoplasty and resection, as was done in one of our cases

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Drs Lamberta, Klopstock and myself have studied the effect of combined streptomycin and P A S therapy in approximately 40 patients in the course of the last year at Triboro Hospital. The basis for such treatment was the conception that this combination of drugs may be able to upset the nutritional-chemical environment in such a way that tubercle bacilli may not become adapted to streptomycin, that is that the emergence of streptomycin resistant organisms may be prevented.

Reports from other sources as well as results obtained at Triboro Hospital seem to confirm the impression that streptomycin-fastness is delayed or prevented if P A S is added to a streptomycin regime. I would like to present some figures, substantiating this impression. In representative cases a total of 62, 84 and 210 grams of streptomycin was given over a period of 133, 84 and 210 days respectively together with a standard dose of six grams of P A S daily. The occurrence of streptomycin resistant strains was either delayed or prevented. In contrast to this 50 per cent of a group of 70 patients given streptomycin alone showed resistant organisms at the end of a six week course and only 25 per cent of germs isolated were sensitive to less than 25 micrograms of streptomycin.

Even though statistical data are not available yet, it appears that delay or prevention of streptomycin-fastness is a frequent, if not a constant feature of combined P A S and streptomycin therapy. In our experience this combined therapy has occasionally given dramatic results.

CASE REPORTS

Case 1 A young colored girl developed a massive hematogenous post-pneumonectomy spread while under streptomycin. She was running a spiking temperature up to 105 degrees F, she went on spreading rapidly even though she was receiving one gram of streptomycin daily, she was in an oxygen tent and the prognosis was entirely hopeless. One week after addition of P A S to the streptomycin regime the temperature subsided, today she is afebrile, not dyspnoic and is able to be up and about. The degree of involvement and the rate of progression of the disease were such that spontaneous remission is difficult to conceive and it appears that in this case P A S was actually lifesaving.

Case 2 A patient with a completely destroyed right lung and progressive cavitory disease on the contralateral side did not show any significant response to conventional streptomycin therapy. A prolonged course of PAS and streptomycin brought about arrest of progression on the left and eliminated all clinical symptoms. The sputum has remained negative on numerous examinations, whereas before it had been persistently positive. As a rule, however, x-ray changes observed are slight and are not at all proportionate to the improvement of the patient's general condition.

Case 3 This patient's pulmonary tuberculosis was of many years' standing. A left pneumothorax had resulted in an inexpandable lung and following pregnancy a massive flare-up occurred on the contralateral side. Eventually a left decortication and a right thoracoplasty were performed and she had several courses of streptomycin which had left her streptomycin resistant.

A few months after the decortication two large cavities developed in this lung, the sputum turned frankly positive on smear and she started suffering frequent febrile episodes, probably due to sputum retention. A double cavernostomy was performed and daily application of PAS to both cavities was started. Two weeks following the cavernostomy the scanty secretions were negative for tubercle bacilli on both concentrates and cultures and so were all gastric lavages. After one month of such local treatment PAS became unavailable for awhile and a distinct increase in the amount of daily secretions was noticed. Reinstitution of local PAS treatment resulted in disappearance of secretions. For the last three months no PAS has been used and the small residual cavities have remained sterile.

Acknowledgement The PAS used in this study was generously donated by Merck and Company and by Panray Company.

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Thank you for your kind invitation to attend this meeting and to take part in the discussion. First I want to congratulate Dr Sweany on his fine presentation of the treatment of pulmonary tuberculosis with PAS. The results are similar to those we have achieved in Sweden—in fact, some of Dr Sweany's patients showed a more dramatic improvement than I have seen.

In Sweden we have made a follow up of 378 cases of pulmonary tuberculosis treated with PAS in six sanatoria. If I should compare the results with those achieved in this country with streptomycin, I would say, that we have seen a faster decrease in temperature and sedimentation rate during PAS treatment, whereas the resolution of the pulmonary lesions seems to go faster during streptomycin treatment. The frequency of conversion of sputum is about the same with the two drugs, the later observa-

tions however are much better with PAS—presumably due to the low frequency of emergence of resistance to PAS

Recently it has been shown in this country, that PAS in combination with streptomycin depresses the frequency of emergence of resistance to streptomycin—both in vitro and in clinical trials. Therefore, a combined therapy seems advisable. However, to be able to evaluate the effect of such a combination we must know the effect of each of the drugs *per se*. I am therefore glad to see that Dr. Sweany has started the treatment with PAS alone in this country, where you have an extensive experience with streptomycin therapy and therefore can better evaluate the different forms of therapy.

The Effect of Streptomycin with Para-Amino Salicylic Acid on the Emergence of Resistant Strains of Tubercle Bacilli^{1 2 3}

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In order to determine the effects of combined streptomycin and para-aminosalicylic acid therapy on the emergence of resistant strains of tubercle bacilli, 11 patients received both drugs for 120 days from July, 1948 to January, 1949. None had received previous streptomycin or para-aminosalicylic acid therapy. Cultures for tubercle bacilli were taken every two weeks and determinations of sensitivity made on all those which were positive.

Clinical Material All patients were white males with far advanced active pulmonary tuberculosis. Nine were between 51 and 58 years of age, one was 49 and the youngest was 38. Streptomycin, 1.0 gm intramuscularly and para-aminosalicylic acid, 15.0 gm, administered orally in three equal doses per day were prescribed for 120 days.

Response to Treatment (Roentgenographic) Patients were selected whose roentgenograms showed components suggesting that they would probably contribute positive cultures for the duration of the treatment period. A comparison of roentgenograms at the beginning and end of treatment showed moderate improvement in four, slight improvement in five and no appreciable change in two. It cannot be definitely stated that the changes observed could not have been obtained by streptomycin therapy alone.

Clinical Observations The beneficial effects of streptomycin on cough, sputum, temperature and weight are well known.⁷ However, the "tonic effect" which is usually apparent soon after beginning treatment with streptomycin was not evident as a result of the

¹Read before the Seventh Veterans Administration Streptomycin Conference, Denver, Colorado, April, 1949.

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³Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions of the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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diffuse gastro-intestinal discomfort produced by para-aminosalicylic acid

Weight The weight gains at the end of treatment were disappointing except in two patients who gained 29 and 6 pounds respectively. The weight in five patients remained unchanged, four lost approximately 6 pounds each. This was in marked contrast to the 20 pound average weight gain in patients with exudative disease previously treated at this institution with streptomycin alone.⁸ An explanation of the difference lies in the fact that during the early months of treatment most patients had a diarrhea attributable to para-aminosalicylic acid with resultant weight losses up to 15 pounds. This was, in most patients, regained during the second half of the treatment period when gastro-intestinal symptoms became less prominent.

Temperature In nine patients, temperature remained normal throughout treatment. In one patient with 100.4 degrees fever at the start of therapy, defervescence took place within the first week and remained normal. The eleventh patient had a temperature elevation to 100 degrees from the third to the fourth month of treatment. A rise in temperature did not occur in any of the patients when the drugs were discontinued.

Laboratory Data

Sedimentation rates All of the patients had elevated sedimentation rates before therapy was instituted. These ranged from 21 mm to 30 mm per hour (Cutler Method). The rate dropped to 11 mm per hour in two patients and remained substantially unchanged in nine.

Sputum Conversion At the end of therapy concentrated sputa specimens were negative for tubercle bacilli in four of the eleven patients. By performing repeated sputa examinations it was possible to obtain at least one positive sputum from each patient so that final sensitivity studies could be performed. However, the four patients have subsequently remained negative on concentration and gastric lavage cultures. Tracheal washings were not performed.

Sensitivity Tests Tubercle bacilli obtained from each patient just prior to the institution of treatment were inhibited *in vitro* by less than 10 mcg streptomycin per milliliter of medium. Sensitivity studies after 60 days of combined therapy showed that the bacilli were still sensitive in all 11 patients. The data from the Seventh Streptomycin Conference, Denver, Colorado, April, 1949,⁹ relative to resistance studies in patients treated with combined therapy, comprised 34 patients. After 45 days of treatment, resistance studies in 22 patients showed only one developing resis-

tant bacilli, after 60 days of treatment, resistance studies in 26 patients only showed three or 12 per cent developing resistant bacilli. On the other hand, the data compiled from a large series of patients using streptomycin alone showed 50 per cent with resistant strains after 60 days treatment. The results were consistent and regardless of whether the patients were treated with 1.8, 1.0 or 0.5 gm streptomycin daily. This apparent delay in the emergence of resistance is further suggested by comparison data for the second, third and fourth months of treatment as given in the table below.

Development of Resistance by Tubercle Bacilli to Streptomycin

STREPTOMYCIN REGIMENS	MONTHS OF TREATMENT		
	2nd	3rd	4th
1.8 - 2.0 gm SM/120 days	50%	66%	74%
1.0 gm SM/120 days	49%	59%	63%
0.5 gm SM/120 days	47%	63%	77%
1.0 gm SM & PAS/120 days	12%	16%	42%

The clinical importance of using antimicrobial agents to prevent or delay the occurrence of resistant micro-organisms is obvious. Comparison of the results of this investigation with reports on the emergence of streptomycin resistant strains of tubercle bacilli when streptomycin alone was administered in the treatment of tuberculosis suggests that combined therapy delays the emergence of such resistant strains. This delay in the emergence of resistant strains by using combined therapy has also been suggested in a preliminary report from the Division of Experimental Medicine, Mayo Foundation with the use of streptomycin, para-aminosalicylic acid and promin.¹⁰

Toxic Manifestations

Renal Irritation. No patient displayed any diminution in kidney function. Five patients excreted urinary casts at some time during the therapy period, but their appearance was transitory. In three a trace of albuminuria was observed but despite continuation of therapy, it disappeared.

Allergic Manifestations. Intermittent eosinophilia of from 6 to 14 per cent was noted in seven patients. Dermatitis appeared in two patients.

Para-aminosalicylic Acid Toxicity. With a daily dosage of 15 gm para-aminosalicylic acid, an average blood level of 3 to 7 mgm per cent was obtained four hours after the oral dose (Ehrlich

Method) Unfortunately, a study of our data does not permit a definite conclusion as to whether para-aminosalicylic blood levels should be maintained for therapeutic efficacy as in the case of sulfones, or whether they need not be constant, as with streptomycin therapy

Diffuse gastro-intestinal discomfort and diarrhea were disturbing factors during the early weeks of treatment. The addition of equal parts of sodium bicarbonate was helpful in reducing the gastric irritation. The Swedish workers have employed a "granule" preparation of the drug with an enteric coating.

Because of the close structural similarity of para-aminosalicylic and salicylic acid, several prothrombin times were determined on four of the treated patients. These were normal.

Para-Aminosalicylic Acid (PAS)

Lehmann,¹¹ Vallentin,¹² and Alin and Difs¹³ have described preliminary observations on the use of para-aminosalicylic acid in human tuberculosis. According to their reports, PAS appears to have a definite chemotherapeutic effect in human tuberculosis.

Youmans¹⁴ has examined the combined effects of streptomycin and para-aminosalicylic acid in experimental tuberculosis in mice. Combination of the two drugs resulted in a better therapeutic response than when either was given separately.

The synergistic action of the drugs in combination, plus the suggested delay in the emergence of streptomycin resistance, is of great clinical importance.

Two additional questions appear of some interest: (1) Are streptomycin-resistant bacilli sensitive to para-aminosalicylic acid? (2) Do tubercle bacilli develop resistance to para-aminosalicylic acid?

PAS sensitivity studies were performed, *in vitro*, on streptomycin resistant tubercle bacilli from 34 patients. The results showed that in each case, growth was inhibited by concentrations of 0.2 mgm per 100 cc para-aminosalicylic acid or less. All cultures tested were obtained from sputa except in two patients from whom pleural fluid and material from a draining sinus were used. It is concluded that streptomycin-resistant tubercle bacilli are sensitive to para-aminosalicylic acid *in vitro*.

Para-aminosalicylic acid sensitivity tests were performed after 120 days therapy in the 11 treated cases; they showed that in six patients, tubercle bacilli were inhibited by 0.3 mgm per cent or less, in two, they were inhibited by 5 mgm per cent, and in three they were not inhibited by 20 mgm per cent. This indicates that resistance to para-aminosalicylic acid may develop.

SUMMARY AND CONCLUSIONS

In a pilot study to observe the rate of development of resistant strains of tubercle bacilli by the use of streptomycin and para-aminosalicylic acid, it appears that development of such strains is delayed

Streptomycin-resistant tubercle bacilli are sensitive to para-aminosalicylic acid *in vitro*

Strains of tubercle bacilli in three patients appeared to develop resistance to para-aminosalicylic acid This matter needs further investigation

Fifteen grams of para-aminosalicylic acid per day caused gastro intestinal disturbance with nausea, emesis and diarrhea Blood levels ranged from 3 to 7 mgm per cent four hours after PAS administration Whether certain specific blood level maintenance is required for therapeutic efficacy requires further study Prothrombin time was not altered by the above dosage

RESUMEN Y CONCLUSIONES

En un estudio preliminar para observar el grado de desarrollo de las cepas resistentes a la estreptomicina después del uso de esta y del ácido para-amino-salicílico, parece que tal desarrollo es demorado

Los bacilos estreptomycinorresistentes son sensibles al ácido para-amino-salicílico *in vitro*

En tres enfermos se encontró que sus cepas de bacilo tuberculoso desarrollaron resistencia al ácido para-amino-salicílico Esto necesita una investigación ulterior

Las dosis de quince gramos de ácido para-amino-salicílico por día provocaron trastornos gastro-intestinales con náusea, vómitos y diarrea

Los niveles en la sangre variaron de 3 a 7 mg por ciento Para determinar si para obtener resultado terapéutico se requiere cierto tenor de la droga en la sangre, se necesita estudio mas prolongado

El tiempo de protrombina no fué alterado por la dosificación señalada

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The Occurrence of Tubercle Bacilli Resistant to P-aminosalicylic Acid (PAS)

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The demonstration by Youmans and associates¹ of streptomycin-resistant tubercle bacilli in eight of 12 patients in the first clinical trials of this drug was soon followed by reports from many other workers showing that streptomycin-resistant tubercle bacilli regularly occur in a certain percentage of patients receiving this antibiotic. The occurrence of streptomycin-resistant tubercle bacilli is now a well-known problem and is the subject of much publication. In contrast, however, is the situation with regard to para-aminosalicylic acid (PAS). In spite of the extensive use of PAS in experimental and clinical tuberculosis since 1946, when Lehmann² first described the tuberculostatic properties of this agent, there has been very little written on the subject of PAS-resistant tubercle bacilli.

Most of the few reports on the *in vitro* sensitivity of human tubercle bacilli to PAS indicate that human tubercle bacilli are sensitive to a low narrow range of concentration of PAS. Youmans,³ using Proskauer and Beck liquid medium, found that 12 strains of human tubercle bacilli, of which six were streptomycin-resistant, were sensitive *in vitro* to concentrations of PAS between 0.019 and 0.156 mg per 100 ml of medium. Sievers,⁴ who used a modified Pryce slide culture procedure, reported that the tubercle bacilli in sputum and from pure cultures were all sensitive to PAS in concentrations ranging from 0.0153 to 0.153 mg per 100 ml of medium. Youmans and associates⁵ augmented their previous observations and found that 17 cultures of human-type tubercle bacilli, of which six were streptomycin resistant, and one bovine strain of tubercle bacilli were all sensitive *in vitro* to 0.156 mg or less of PAS per 100 ml of medium. Most of the strains were inhibited by less than 0.039 mg of PAS per 100 ml of medium. We⁶ have used egg-yolk agar medium containing sodium para-

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aminosalicylic acid (NaPAS) in twofold dilutions ranging from 0.006 to 6.4 mg of NaPAS per 100 ml of medium and have reported that cultures from 71 patients who had not received PAS were sensitive to 0.012 to 0.025 mg of NaPAS per 100 ml of medium.

Hurni⁷ found that two of four freshly isolated strains of human-type tubercle bacilli could be made to grow in 30,000 times the original concentration of streptomycin after four passages in Dubos' medium containing the antibiotic. The other two strains required nine passages before showing ability to grow in high concentrations of streptomycin. For PAS, however, it required eight passages before growth was seen in as much as ten times the original concentration of PAS. Hurni did not consider this to be true PAS resistance and stated that if resistance to PAS does develop at all it does so very slowly as compared to streptomycin resistance. Sievers⁸ reported that tubercle bacilli will not continue to grow in concentrations of PAS greater than 0.015 mg per 100 ml of medium using the slide culture technique and that he had not observed any consistent resistance to PAS in numerous specimens from patients treated with this substance. Eastlake and Barach⁹ found that cultures from untreated patients were resistant to only 0.078 mg of PAS per 100 ml of medium but that cultures from three other patients who had received 210, 630 and 1,000 gm of PAS respectively were resistant respectively to 2.5 mg, 0.63 mg and 0.63 mg of PAS per 100 ml. They stated that either strains vary in their sensitivity to PAS or else some degree of resistance did develop.

Widstrom and Swedberg,^{10, 11} using Dubos' medium, reported finding a considerable difference in sensitivity to PAS among various strains of tubercle bacilli. They found that a number of human-type strains and the Ravenel bovine strain were resistant to at least 10 mg of PAS per 100 ml of medium. Swedberg and Widstrom^{12, 13} have also written that no beneficial effect of PAS therapy could be seen in mice infected with the PAS-resistant Ravenel strain. Widstrom and Swedberg^{11, 14} have found that PAS-resistant cultures of tubercle bacilli may be isolated from some patients after prolonged treatment with this substance and that mice infected with such strains will not respond to treatment with PAS. Sweany¹⁵ stated that "we have found in from 5 to 10 per cent of our treated cases an unstable type of bacillary resistance to PAS which fluctuates considerably. About half of these cases developed a complete resistance to 10 mg of PAS per 100 ml of medium and showed a corresponding deterioration of the patient's clinical course. Some of the other patients who have shown slight or partial resistance to 10 mg of PAS have made considerable clinical improvement. The final evaluation of this phenom-

enon is not yet possible" Odelberg¹⁶ reported that in a series of 79 patients treated with PAS for at least 184 days five were found to have PAS-resistant tubercle bacilli. These patients were treated with PAS at the rate of 10 to 15 gm daily with a short period of three to four days of no treatment every five weeks. They also received a short course of streptomycin therapy of 1 gm a day for one to two weeks only. Dunner and associates¹⁷ reported that PAS-resistant tubercle bacilli were found after treatment in three of 11 patients who received 15 gm of PAS and 1 gm of streptomycin daily for 120 days.

We⁶ previously reported finding PAS-resistant tubercle bacilli in four of five patients treated with PAS alone for periods of 157 to 251 days. These cultures were able to grow in medium containing 200 to 500 times as much NaPAS as was required to inhibit the growth of cultures isolated from the same patients before treatment was started. Two of these patients had streptomycin-resistant tubercle bacilli prior to treatment with PAS and the cultures finally isolated were resistant in vitro to both antituberculosis agents. Of particular interest was the finding that there was no demonstrable increase of resistance to streptomycin or to PAS in the case of four patients who were treated approximately the same length of time with PAS, streptomycin and promin. An in vivo test in guinea pigs using a PAS-sensitive tubercle bacillus and a PAS-resistant strain from the same patient showed that no favorable therapeutic effect was caused by treatment with PAS in the infection due to the PAS-resistant strain, in contrast to the beneficial effect of the treatment in the animals infected with the PAS-sensitive strain.¹⁸

We have extended our studies on the in vitro sensitivity to PAS of tubercle bacilli isolated from patients who had not received PAS and from patients treated with PAS alone or in combination with streptomycin and promin. The data to be presented include our previously published observations.^{6, 19}

Methods

The in vitro tests were done with egg-yolk agar medium²⁰ containing four fold concentrations of PAS ranging from 0.0045 mg to 4.608 mg per 100 ml of medium. Higher concentrations were used in some instances when cultures were found to be resistant to more than 4.608 mg per 100 ml. We have found that the differences in the amount of growth are more easily detected on this solid medium than in liquid medium. Furthermore, it is possible to select single colonies from solid medium for further study. The medium is easily prepared by adding the yolk of one egg to 120 ml of sterile melted and cooled nutrient agar. Because

of its greater solubility a calculated amount of NaPAS is used to give the desired amount of PAS (Previously we expressed PAS sensitivity in terms of the concentration of NaPAS $2H_2O$ but to conform to the usage of others we now express the concentration in terms of the actual amount of PAS) The desired solutions of NaPAS are sterilized by filtration and added to the melted nutrient agar immediately before the egg yolk is added (It is more practical to sterilize by filtration the most concentrated solution to be used Fourfold dilutions can be made from the single sterile solution by using sterile distilled water) The nutrient agar, NaPAS and egg yolk are mixed by shaking and then poured into sterile test tubes which are placed in the slanted position to harden

The inoculum is prepared by grinding in a mortar several loopfuls of the culture to be examined and adding enough sterile water to make a suspension approximately equivalent to 1 mg per milliliter The accuracy of making this suspension is not critical, for we have found that a tenfold variation in the concentration of tubercle bacilli will not significantly affect the results Each tube of medium containing PAS plus a control tube is inoculated with 0.1 ml of the suspension After 14 days of incu-

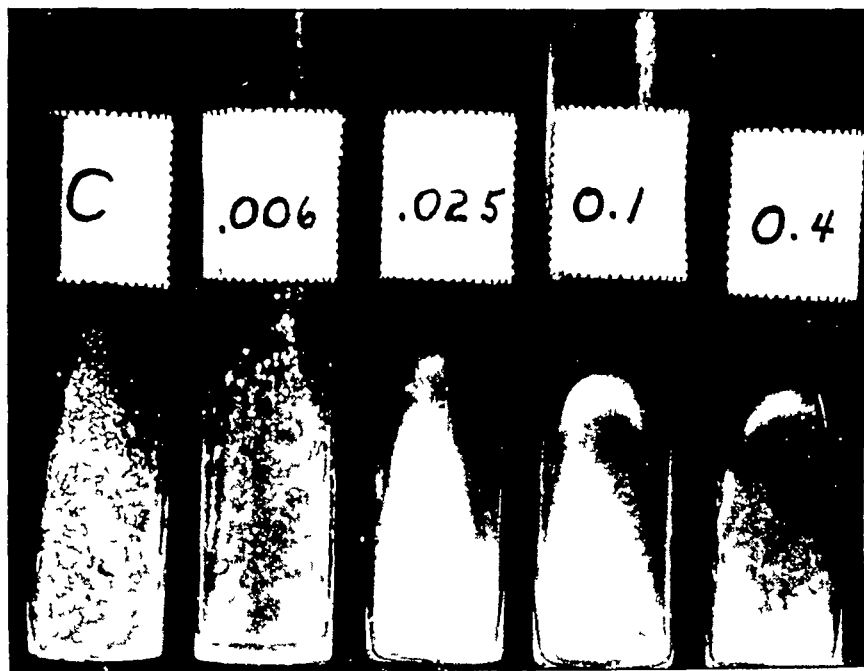


FIGURE 1 PAS sensitive culture after 28 days of growth The concentration of PAS per 100 ml of egg-yolk agar is indicated on each tube After 14 days of incubation there was luxuriant growth on the control tube only and the resistance to PAS was recorded as ≤ 0.006 After an additional 14 days of incubation, growth appeared only on the tube containing 0.006 mg of PAS per 100 ml of medium

▲Signifies "less than"

bation the resistance of the culture to PAS is recorded as the maximal concentration which permits growth

We formerly recorded the results after 14 days and again after 28 days of incubation and found that there was no significant increase in the amount of growth. At most there was growth only in the tube containing the next highest concentration of PAS after an additional incubation of 14 days

Results

Including those previously reported⁶ we have examined 107 cultures of human-type tubercle bacilli and two cultures of bovine tubercle bacilli. All of these, including 15 human-type cultures which were resistant to streptomycin, were sensitive to a low narrow range of concentration of PAS. Ninety-five per cent of the human type cultures were resistant to only 0.018 mg or less of PAS per 100 ml of medium. Four were resistant to 0.072 mg and 1 culture gave good growth in medium containing 0.144 mg of PAS per 100 ml of medium. The two bovine strains were resistant to not more than 0.018 mg of PAS per 100 ml of medium. The variations that did occur were represented by differences in growth on one or two tubes which, upon repeated tests, were

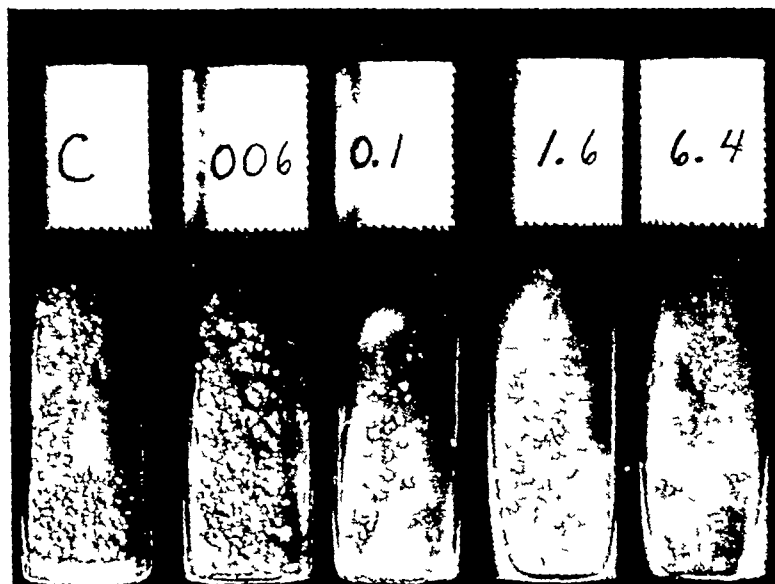


FIGURE 2 PAS-resistant culture from patient 7 in table 1. The growth on the tube containing 6.4 mg of PAS per 100 ml of medium was subsequently found to be resistant to more than 32.8 mg of PAS per 100 ml. The difference in the amount of growth on the control tube and on the higher concentrations of PAS suggests that there may be a mixture of PAS-sensitive and PAS-resistant bacilli.

found to be within the limits of accuracy of the procedure Figure 1 shows the results of a test on a culture from a patient who had not received PAS

Our experience with patients treated with PAS alone for prolonged periods is limited to 8 cases From four of these it was possible to isolate tubercle bacilli which were resistant in vitro to high concentrations of PAS, as shown in Table 1 This group is too small to allow for any conclusions regarding the incidence of the occurrence of PAS-resistant tubercle bacilli Clinical studies are too limited to date to determine the correlation between the sensitivity of the strains in each case and the response to therapy It is unfortunate that a culture was not obtained for sensitivity tests prior to therapy from patient two, but it may be assumed that the culture was probably not unlike other cultures from patients who have not received PAS Figure 2 shows a PAS-sensitivity test on a culture from patient seven in Table 1 The growth on the tubes containing PAS is less than that on the control, suggesting that there is a mixture of PAS-sensitive and

TABLE 1
In Vitro Resistance to PAS of Tubercle Bacilli Isolated From
Patients After Extensive Treatment With PAS

Patient s number	Duration of treatment days	Approximate daily dose gm	Total dose gm	Resistance to PAS*	
				Before treatment	After treatment
1†	90	**	2,096	Not done	0 004
2†	267	8 to 10	2,250	Not done	4 608
3†	131	2 to 10	391	0 072	1 150
4	165	9 6	1,760	0 004	0 004
5†	183	8 to 10	1,650	0 004	2 300
6	96	10 to 15	1,020	Not done	0 004
7§	185	10	1,850	0 004	6 4††
8§	248	10	2,480	Not done	0 004

*Maximal concentration of PAS in milligrams per 100 ml of medium which permitted growth

†Cultures from these patients were resistant to streptomycin before PAS therapy was started

**Up to 30 gm of NaPAS intravenously per day with 14 4 gm of PAS orally during the last 30 days

§These patients received 1 gm of streptomycin daily plus 10 gm of PAS daily for one month, followed by treatment with PAS alone for five months

††This culture was used to infect mice and when reisolated from the animals it was found to grow in 32 8 mg of PAS per 100 ml of medium

§Signifies "greater than "

PAS-resistant tubercle bacilli. The final cultures from patients two and five were tested on medium containing streptomycin and PAS and were found to be resistant in vitro to both agents.

Table 2 presents observations made on a series of patients treated with PAS, promin and streptomycin. Each patient received 0.5 gm of streptomycin once daily, 5 to 10 gm of PAS daily in four divided doses and 5 gm of promin intravenously per day for the first 14 days of each 21-day period, except for patients 15 and 16 who received no promin.

Only patient 10 was found to have streptomycin resistant tubercle bacilli after the combined treatment. Even though the series is small, this is much lower than the number of patients who would be expected to discharge streptomycin-resistant tubercle bacilli after treatment with streptomycin alone.¹⁸ Of particular interest are the results of the tests for resistance to PAS. Again the series is too small to permit conclusions and the series treated with PAS

TABLE 2

The Effect of Combined Treatment With PAS, Streptomycin and Promin on the Emergence of Streptomycin-resistant and of PAS-resistant Tubercle Bacilli

Patient's number	Duration of treatment days*	Resistance to Streptomycin		Resistance to PAS	
		Before treatment	After treatment	Before treatment	After treatment
9	104	1 0	1 0	Not done	0 072
10	180	1 0	1,000	0 072	0 018
11	180	1 0	1 0	Not done	0 004
12	90	Not done	1 0	0 004†	0 004
13	145	1 0	1 0	0 004‡	0 004
14††	90	1 0	1 0	0 004	0 004
15§	180	1 0	1 0	0 004	0 004
16§	180	1 0	1 0	0 009	0 018
17	97	1 0	1 0	0 018	0 018
18	129	1 0	1 0	0 036†	1 60

*Streptomycin 0.5 gm once daily, PAS, 5 to 10 gm orally in four doses daily, promin 5 gm intravenously daily for 14 days of each 21-day period.

†Culture obtained three weeks after treatment started.

††PAS discontinued after 90 days. Streptomycin and promin continued for an additional 90 days, at which time a culture was found to be resistant to streptomycin.

§Received no promin.

‡Signifies "greater than."

†Signifies "less than."

alone (Table 1) is too small for comparison. The data suggest, however, that combined therapy may prevent or delay resistance to PAS. This, of course, can be determined only by studies on much larger groups of patients. Observations on 11 other patients being treated with streptomycin, PAS and promin are not included in Table 2 because none of them have been treated for longer than 60 days. In none of these 11 patients have streptomycin-resistant or PAS-resistant tubercle bacilli been demonstrable.

Comment

The method of detecting PAS-resistant bacilli in our studies was chosen merely because we routinely use egg-yolk agar for streptomycin-resistance studies. We prefer a solid medium because differences in the amount of growth are readily seen and because it is possible to select individual colonies for further examination. We have not made a comparison of the various culture procedures that may be used for studying the in vitro sensitivity of tubercle bacilli to PAS, but obviously such a comparison is needed. A standard procedure should be developed and adopted by various workers in order that comparable data may be secured.

The significance of our findings and those of others that tubercle bacilli with an increased resistance to PAS may occur in patients treated with this compound is not known and must await the results of extensive clinical observations correlated with laboratory studies. It is essential that the sensitivity to PAS be determined for cultures obtained from patients prior to, during and after treatment.

The results of studies on cultures of tubercle bacilli from untreated patients suggest that various strains are sensitive in vitro to a low narrow range of concentration of PAS. If, however, it is eventually found that there is a considerable variation in sensitivity to PAS and that cultures having a certain degree of resistance in vitro are also resistant in vivo, it will be necessary to test cultures from every patient before PAS therapy.

Summary

One hundred and two cultures of human-type tubercle bacilli from patients who had not received PAS were found to be resistant to 0.018 mg of PAS per 100 ml of egg-yolk agar but not to 0.072 mg. Four cultures were resistant to 0.072 mg and one to 0.144 mg per 100 ml of the medium. Cultures from four of eight patients treated with PAS alone for prolonged periods (90 to 267 days) were able to resist the inhibitory action of PAS at concentrations greatly in excess of that required to inhibit the growth

of strains from untreated patients. In a group of 10 patients treated with streptomycin, PAS and promin, only one was found after treatment to have streptomycin-resistant tubercle bacilli and one other had PAS-resistant tubercle bacilli.

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Cavernostomy and Tamponade of Pulmonary Cavities with Para Aminosalicylic Acid*

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The pulmonary cavity is the *focus* considering the campaign against tuberculosis. The cavity decides the patient's fate and dominates the epidemic state of tuberculosis. The persistence of the destructive lesions perpetuates the source of infection.

Of people in whom sputum tubercle bacilli are found, more than 50 per cent die within 10 years of the discovery, in spite of collapse therapy and sanatorium care. This has been so up to the present, and the future will show how much antibiotics and chemo-therapeutics will be able to reduce this alarming mortality.

Streptomycin is generally effective in hyperaemic foci such as specific meningitis, laryngitis, bronchitis and some forms of intestinal tuberculosis. On the other hand, foci whose blood supply is reduced by local thrombosis, such as a caseous lung infiltration or a cavity wall, are as a rule not affected by streptomycin or para-aminosalicylic acid. Ulcerations of the larynx or of the intestines may heal, whereas the lung cavity, which has provoked it, will remain and may cause further disseminations in the lung or elsewhere. A second, even a third course of treatment must then be undertaken which is likely to end with the development either of toxic symptoms in the patient or streptomycin resistance in the tubercle bacillus. Therefore the tuberculous cavity remains the deciding factor in the survival of the patient and the perpetuation of the epidemic state in spite of antibiotics and chemo-therapeutics.

Taking into consideration the reduced permeability of the cavity wall and its poor blood supply, we introduce an adapted procedure. The three essential phases of the method are:

- 1) The gradual establishment of the cavernostomy by means of laminaria sticks, that is a "stoma" between the skin and the cavity.
- 2) The regular packing of the cavity with gauze, soaked in streptomycin or P A S.
- 3) The closure of the draining bronchus by means of diathermy, applied through an operating thoracoscope.

The draining bronchi of the cavity are generally open. If they appear to be closed, it is our experience that in active and suppurative cases this closure is fictitious and not a true one in the

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anatomic-pathological sense. It is no question of a real fibrotic obliteration, but the bronchi can be blocked by specific granulation tissue. On this error is based Monaldi's method and it explains its failure.

We tried a "Cavernostomy" the first time at the beginning of 1947 on two cases which had to be considered as lost. The intervention had been carried out with improvised instruments. Both patients are perfectly healthy today. The construction of the definite equipment for the tamponade of lung cavities took a whole year, so that further patients could only be treated since March 1948.

According to the usual resources of tuberculosis therapy out of 38 cases, 30 had to be considered as hopeless. For the 8 others thoracoplasty would have been indicated, but the intervention was refused. The secretion of all the cavities, treated with our method, became and remained free from tubercle bacilli and that on an average of 17 days after the first streptomycin or P A S tamponade. Later, the expectoration became negative if no other destructive foci were present. 28 patients became free from tubercle bacilli in the sputum. The other 10 had been the most desolate cases, yet cavity secretion became negative, but expectoration remained positive. Even these patients have improved in an astonishing way, temperature became normal, symptoms of toxic cardiac disturbances disappeared so much that thoracoplasty or a second cavernostomy on the same or on the contralateral side became possible.

Of course the method was at the beginning purely theoretical and experimental and we had therefore morally no right to try it on patients who had a chance of recovery with the already established therapy. Therefore the modest number of cases. *We had to fear complications from the gradual dilatation of the cavernostomy channel* as a rapid aggravation of the destructive lesion itself, or disseminations, or mortal haemoptosis, all this provoked through the unavoidable traumatism of the cavity.

Fortunately *no fatal complications* occurred and all the patients are alive today, some of them leading a normal life, and the others have a good prognosis. It is impossible to judge how many of them would be dead by now without our direct treatment of the cavity. To conclude, our method cannot be considered any longer as theoretical and experimental or even dangerous. As clinical findings show, it is a most promising enrichment for treatment of cavitary tuberculosis.

The complications we have to expect are

- 1) Hemorrhages are seldom, very seldom alarming and easily

stopped by packing of the bleeding cavity with gauze soaked in Thrombin "Roche "

2) Fresh infiltrations around the cavity with a high but short rise of temperature In one case lobal pneumonia developed but entirely resorbed in 12 days

3) In four cases there was severe irritation of the cavity, the trachea and the larynx, provoked by gauze-packing with a soiled preparation of para-aminosalicylic acid These four patients recovered, the cavities closed and the sputum became negative But in Dublin a cavernostomy case, on the way to recovery, died in a delay of 48 hours after a tamponade with a bad preparation of P A S

A dangerous run in the international market of P A S has started, serious for patients and bad for the reputation of our method According to our researches the P A S of Dr Wander, Berne, the so-called "*Aminacyl*" in a solution of 5 per cent has no noxious influence on lung tissue and yet is highly efficacious I therefore recommend this preparation of para - aminosalicylic acid If Aminacyl is not available we better make the gauze-packing with 0.1 gr streptomycin in 20 cc of physiological solution Besides this local application we give 0.5 gr streptomycin intramuscularly or Aminacyl tablets

The internal opening of our *big calibre rubber tubes* touches often the cavity wall, which hinder the discharge of pus, even more, through a sucking action we imitate the phenomenon of a cupping glass and irritate the cavity wall or risk hemorrhages For this reason we recently have not made any draining with sucking action

While coughing, the cavity pus is thrown out directly into a little waterproof bag, fixed on the tube In this way we avoid, for the discharge of the cavity secretion, the detour over the bronchial system, we have less poisoning Bronchial and larynxulcerations have a better chance to heal thanks to this "short-circuit-expectoration" where the cavity tube is acting like a trachea

Only with gauze-packing does all of the cavity wall get into intimate contact with streptomycin or P A S The repeated instillation of the fluid on the gauze end assures the continuity of the direct application, because the gauze acts like a wick Practically we imitate in some way the treatment of tubercle bacilli in a test glass and so the revolutionary therapeutic effect finds its explanation, the sterilization of cavities on an average of 17 days

By regular *cavernoscopy* we are able to follow the improvement as clearly as the healing of tuberculosis in the eye with the ophthalmoscope After the first few tamponades, the cavity wall

looses its caseous aspect, becomes smooth, has more and more blood supply and becomes highly hyperaemic. The permeability is increasing and so tubercles next to the cavity are now influenced by the sterilizing effect of P A S.

The closure of the draining bronchus Specific granulation tissue of the draining bronchus may be gradually sterilized, then more and more substituted by fibrotic cells and the consequent retraction may finish in a real closure, that is a fibrotic obliteration of the bronchus. This has to be verified by cavernoscopy control, colored liquid and radiological contrast.

If the bronchus does not obliterate, we coagulate its opening with high frequency current (usually several sessions are necessary). A diathermy scurf never detaches but is substituted by fibrotic tissue and again by the consequent retraction we finally obtain the desired obliteration of the bronchus.

The finish of the treatment Instead of the periodical dilatations of the cavernostomy and repeated tamponades, we let retract the stoma more and more. Once a last and thinnest drain is extracted, the remaining fistula closes at once. The scar left in the skin is not bigger than a pea.

CONCLUSIONS

Therapeutical out-look Desolate cases may become curable. *Lobectomy for cavitary tuberculosis* without, before or after thoracoplasty, as a rule will be superfluous. Giant cavities or, destructive lesions, badly situated with a view to collapse therapy, shrink by preliminary cavernostomy, so that finally the thoracoplasty becomes possible and efficacious. In the usual indication field of thoracoplasty the plasty may be avoidable in a way that some of these cases recover by an accessory phrenic nerve crush plus pneumoperitoneum, and others by cavernostomy alone. Pregnant women with cavitary tuberculosis may recover and have a healthy baby.

And even more, considering the epidemic aspect, the public health as well as state economy, the method seems to be of value.

CONCLUSIONES

Los casos desesperados pueden convertirse en curables. La lobectomía para la *tuberculosis cavitaria*, sin, antes o después de toracoplastia, como regla será superflua. Las cavernas gigantes o las lesiones destructivas, mal situadas por lo que se refiere al colapso, se reducen por la cavernostomía previa de manera que la toracoplastia finalmente se torna posible y eficaz. En el campo habitual de las indicaciones de la toracoplastia, puede en cierto modo ser evitable ya que ciertos casos se recuperan por una frenopraxis accesoria más neumoperitoneo y otras por la simple cavernostomía.

Las embarazadas con tuberculosis cavitaria pueden recuperarse y dar a luz un producto sano

Y mas aun, considerando el aspecto epidémico, la salubridad publica asi como la economia estatal, el método parece ser de valor

D I S C U S S I O N

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It is a pleasure to discuss Dr Maurer's approach to the control of tuberculous cavities. There is an old axiom that in treating cavities by drainage the successful procedure must provide the means of continuous and complete removal of secretions from the cavity. Packing the cavity with gauze has proved to be an effective means of providing drainage. The use of medications to aid in sterilizing the cavity need not be limited to any particular drug but any chemical which has the power of destroying the germs present may be used. The sulfa drugs were used effectively before the introduction of penicillin and streptomycin.

In the past I have had most satisfaction through the use of open cavernostomy with the placing of skin flaps on the inner walls to aid in obliterating and lining of the residual defect. Various chemotherapeutic agents have been used to aid in controlling any infection present. The following cases give an indication of the type of cavities which we have treated by open cavernostomy. They range from the giant bilateral apical to the mid-lung cavity in a remaining lung after one lung has been collapsed by thoracoplasty.

One important point that must not be overlooked is the necessity of obtaining closure of all bronchi that open into the cavity before allowing the drainage tract through the skin to close. If the skin opening is allowed to close before the bronchial openings are all closed there is frequently a recurrence of the cavity through re-infection by way of the open bronchus.

I am impressed by the results obtained to date by Dr Maurer and shall apply the procedure which he has described in selected cases in my own practice. Again I would issue a word of caution. Do not be too hasty in discontinuing the packing of the cavity—be certain all bronchial openings have closed.

I must commend Dr Maurer on his ingenuity and skill and I would wish for you and me a portion of the patience exhibited by Dr Maurer in the treatment of his patients.

JOHN V THOMPSON, M.D., F.C.C.P.
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It was a privilege to hear Dr Maurer's experiences. He should be commended for his early success in converting the sputa in such a group of poor risk patients. The semi-closed method utilizing a large bore tube would seem to present some problems. I should like to ask Dr Maurer if he has had difficulty with persisting sinuses, fistulae or possibly recurrence of the cavity by this procedure and how he has handled these complications. I have preferred wide open method of cavernostomy.

It should be noted that most of the attempts at open drainage of tuberculous pulmonary cavities reported in the literature were marked by an apparent lack of consideration for the other pulmonary lesions. All cases in the following series were far advanced, bilateral, and of the poor risk type. There were 29 patients in the series under consideration upon whom 31 pneumonotomies were performed. Twenty-four were operated on from two to seven years ago, and all followed to date. Seventeen had a recurrent, new or residual cavity beneath apparent maximum thoracoplasty. Seven patients had a recurrent or residual cavity where thoracoplasty was not maximum, but could not be extended because of bronchial disease, contralateral collapse, unstable contralateral lesion, and other complications. Five had isolated lower lobe cavities over diaphragmatic paralysis.

It would appear that other pulmonary tuberculous lesions, particularly in the regions adjacent to the cavity, probably should be relatively stable or have good possibilities of control. The trauma incident to operation and the contraction of fibrous tissue in obliterating the healing cavity must affect the adjacent lung areas biologically as well as mechanically. In all the patients of this series the lesions adjacent to the cavitation had been brought under at least the partial effect of some collapse procedure.

It was observed that the more widely the cavity was opened to the exterior without cutting excessively into lung tissue, the better it appeared to heal and obliterate. The medial cavity wall was coagulated to destroy it as much as possible. A large skin flap was dissected up superiorly or laterally and the free end sutured to the cavity wall or pleura. These flaps appeared later to keep the wound open and also acted as a point from which epithelization took place over the deeper parts of the wound. Likewise the medial or inferior edge of the skin was sutured to the muscles. The wounds were loosely packed open with gauze.

Recently three cases with tension cavities present were approached in a somewhat different manner. The cavity wall was merely slit open and a skin flap sutured to the cavity wall to act

as a ball valve drainage somewhat similar to the Eloesser flap operation for empyema. These cavities were not packed with gauze. It does not appear that this type of drainage is going to be as satisfactory as the wide open type of exteriorization described above.

The postoperative care consists of a long period of daily light packing with gauze which may be soaked alternately in penicillin, streptomycin, tyrothricin or cod liver oil to keep the wound as clean as possible. Occasional stimulation of the granulations and bronchial fistulae with silver nitrate or the cautery is beneficial. Recently dusting of the depths of the wound with P A S has been done. There has been no remarkable change as a result of this dusting but the wounds do appear somewhat cleaner.

After about nine months of such management, if the wounds do not show signs of becoming healed in the near future, a plastic closure of the defect may be considered. There is apparently too much active infection present to attempt closure before this time in our experience. The wound is prepared for several days with wet dressings and antibiotics are administered and continued post-operatively. A plane of cleavage is established between the granulation tissue and the underlying tissues and the former is bluntly dissected out of the defect. The defect is then obliterated by re-approximating the tissues in layers with chromic c. If a bronchial fistula is present, in addition a pedicled muscle graft is obtained from the adjacent musculature and sutured into the orifice of the bronchus.

Ten plastic closures of sinuses and fistulae were performed. Eight healed promptly and two broke down but later healed. Of the 24 patients followed for over two years, 17 have healed wounds. Seven of which healed spontaneously and 10 were closed by plastic procedures. Three patients have persistent complicated sinuses which might heal spontaneously but will probably require further operative procedures. Four patients are dead. Five recent cases appear to be healing satisfactorily, but have not reached the point yet where the decision between operative closure and spontaneous healing can be made.

Of the 25 living patients in the entire series sputum conversion took place in all. However, three have developed positive sputum again from the appearance of cavitation in the contralateral lung. *Seventy-five per cent* of the patients operated on over two years ago have both negative sputum and healed wound. Excluding the recent cases, all living patients are now working except the three with positive sputum, and two of whom are about to be discharged from the hospital.

One patient, after three years, died of a complicating tuberculous spine, another patient succumbed to a general breakdown of the

tuberculous process, the third patient died from pneumonia after cavernostomy for a cavity in the contralateral lung performed by another surgeon. The other death was caused by an embolism while the patient was undergoing cauterization of a persistent sinus. Mortality thus for the entire series was 13 per cent to-date.

The Treatment of Tuberculosis in Sweden with Para-Aminosalicylic Acid (PAS) · A Review

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Historial Remarks

The tuuberculostatic effect of PAS was discovered by the writer in 1943^{1 3} On the basis of the studies of F Bernheim on the stimulating effect of benzoic and salicylic acids on the respiration of the tubercle bacillus, it was suggested that the introduction of an aminogroup in the salicylic acid molecule in para-position (4-position) should be able to convert the stimulating effect into an inhibitory effect and thereby inhibit even the growth of the bacillus PAS was synthesized by K G Rosdahl at the Ferrosan Company in Malmo, Sweden, in December 1943 and the tuberculostatic effect demonstrated in vitro in the same month

The first clinical trials were conducted by Dr G Vallentin and the writer at Renstroms sanatorium in Gothenburg in March 1944, thus about half a year before the first clinical trials with streptomycin in the United States

PAS was first used in the local treatment of Monaldi fistulas and abscesses, then in hopeless cases of pulmonary tuberculosis and later on in moderate and slight cases (Lehmann¹ and Vallentin⁴) During the following years the Ferrosan Company produced larger quantities of PAS and a team work on the treatment of pulmonary tuberculosis in six Swedish sanatoria was established A report on this work—378 cases—was presented at the conference of the Scandinavian Tuberculosis Association in Copenhagen in 1948 (Vallentin, Tornell, Beskow, Carstensen, Thune, Helleberg and Lehmann⁵)

Chemical Properties, Absorption, Excretion and Toxicity of PAS

PAS is an acid of about the same strength as benzoic acid It is soluble in water only to 0.2 per cent The sodium salt is however soluble to about 96 per cent (Rosdahl⁶) The solubility decreases with decreasing pH These data are of interest for the absorption of PAS because of the slight solubility in acid solution it will only to a slight extent be absorbed in the stomach When successively neutralized in the intestines PAS is dissolved and absorbed PAS is a small molecule and is quickly absorbed and

*From the Central Laboratory, Sahlgrens Hospital, Gothenburg, Sweden

excreted A peroral dose of 4 g of the acid will be excreted within three to four hours, the sodium salt somewhat quicker

The blood concentration is naturally dependent on the speed of absorption and the speed of excretion and will have its maximum after $\frac{1}{2}$ to 1 hour In order to delay the absorption of PAS the Sewdish preparation of PAS* is enteric coated in small granules first dissolving in the small intestines With this preparation the blood will show maximum values first after about two hours and after five to six hours a single dose of four grams is excreted in the urine Repeated doses with an interval of three to five hours is required for a permanent blood concentration

High concentrations of PAS are achieved in the kidney and the urine A daily dose of 14 grams PAS granules (11 grams PAS*) will give a concentration of 300 to 900 mg per cent in the 24 hours urine As such high concentrations are not necessary for the treatment of tuberculosis of the kidney and urinary tract the treatment of these forms of tuberculosis can be done with a lower dose (8 to 10 grams granules)

About half of the PAS in the urine is found in the acetylated form which is not tuberculostatic The PAS not excreted is mainly found in the tissues rich in elastin (Alin and Helander⁷) Due to the high solubility of the PAS in the urine no deposits of PAS are seen in the kidney or urine even after the highest dosage of PAS (20 to 30 gm sodium-PAS per day) See also Alin and Difs⁸

As to the *toxicity* of PAS no damage of the liver, heart or kidney have been seen Intestinal complaints in the form of nausea, vomiting and diarrhea was frequently seen before a suitable coating substance was found Still some sensitive patients react in this way However, after a free interval of four to six days the drug is often tolerated well

Administration of PAS

Different forms of administration of PAS have been tried Permanent *intravenous* infusions (2 per cent) in most cases give rise to thrombophlebitis within three to four days This experience was won with rather impure preparations and possibly the more pure preparations of recent years are better tolerated *Intramuscular* injections have to be given in large repeated doses (10 ml, 10 per cent solution) in order to provide permanent blood concentrations As they are rather painful and PAS is too quickly absorbed and excreted, this form of administration cannot be recommended The *peroral* administration is to be used as the routine method

*The granules contain 30 per cent coating substances Special measures have been used containing ca 22 grams of the granules That is why the doses refer to the granules In the future measures containing 2 grams of the acid will be used—The Ferrosan LTD Malmö 3 Sweden

Intestinal complaints can be treated with interruption of the administration or a few drops of opiate or a teaspoonful of magnesium oxide before PAS is given *PAS should always be given together with or after a meal* or a glass of milk and some bread and butter The granules or dragées should not be chewed

Intralumbar injections of 5 to 10 per cent sodium PAS solutions have been used in cases of meningitis (two times a week in the beginning of the disease) After a few weeks treatment the viscosity of the cerebrospinal fluid increases and makes aspiration impossible—if due to the disease or the injections has not been recognized

Intrapleural injections have been used in the treatment of empyema During the first year 200 to 300 ml 5 per cent solutions were used but later on only 20 to 25 ml 10 to 20 per cent solutions were injected after aspiration once a week according to Dempsey and Logg⁹

For the *local application* of PAS solutions in the treatment of skin-tuberculosis (lupus), fistulas and abscesses 5 to 10 per cent solutions have been used For the use in fistulas and abscesses the viscosity of the solutions was increased as desired by addition of 1 to 2.5 per cent cellugelphosphate PAS in ointments has not been effective (Lemming¹⁰)

Pulmonary Tuberculosis A Comparison with Streptomycin

The greatest experience of the treatment with PAS has been gained in pulmonary tuberculosis In the following an attempt is made to compare the efficacy of PAS as evidenced from the above mentioned team work of six Swedish sanatoria (Vallentin, Tornell, Beskow, Carstensen, Thune, Helleberg and Lehmann⁵) with that of streptomycin as presented by the Army, Navy and Veterans Administration in the *American Review of Tuberculosis*, 56 485, 1947

The PAS material consisted of 378 cases of pulmonary tuberculosis Certain rules were established for the selection of the cases and the treatment The rules were the following

- 1) The diagnosis should be made by a positive culture or guinea pig test just before the treatment or by a typical x-ray together with a positive slide

- 2) The pulmonary process should be progressive or stationary for some months without signs of regression

- 3) Preferably far advanced and moderate cases of exudative as well as proliferative types with or without other complicating localizations of tuberculosis should be treated

- 4) The observation time before treatment should be at least two months with rest in bed and ordinary sanatorium regime

5) Cases treated with collapse therapy were included in the material and not considered to interfere with the estimation of the PAS effect, if the collapse therapy had been finished three months before the PAS treatment was commenced or the collapse therapy had been instituted three months before PAS and the process still showed signs of progression. The collapse therapy should be continued during the treatment as before PAS. No form of collapse therapy should be introduced during the PAS treatment or during the observation time after PAS.

6) The age of the patients should be between 15 and 60 years, preferably between 15 and 35 years.

7) PAS should be given orally with an average dose of 14 gms a day divided into four to six doses. The treatment should be continued at least during one month and if possible without interruption.

8) The observation time after PAS should be at least three months.

9) Certain rules were established for laboratory procedures including erythrocyte sedimentation rate once a week, hemoglobin and count of the white cells every 14 days and sputum examinations and x-ray every month. The patients were weighed once a week or once fortnightly.

TABLE 1
Clinical Material

	S E X				AGE IN YEARS					
	Male		Female		5-15		15-35		35	
	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct
PAS material	99	(48.3)	106	(51.7)	6	(2.9)	151	(73.7)	48	(23.4)
Streptomycin material	219	(98.2)	4	(1.8)	0	(0)	161	(72.2)	62	(27.8)
	Extent of Lesion						Predominant Type of Lesion			
	Minimum		Moderate		Far Adv		Exudative		Proliferative	
	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct
PAS material	10	(5)	41	(20)	154	(75)	122	(59.5)	83	(40.5)
Streptomycin material	2	(0.9)	65	(29.1)	156	(70)	83	(63.4)	48	(36.6)
	C A V I T I E S				COURSE OF DISEASE					
	Present		Not Present		Progressive		Stationary			
	No	Pct	No	Pct	No	Pct	No	Pct		
PAS material	169	(82.4)	436	(17.6)	184	(89.7)	39	(10.3)		
Streptomycin material	182	(81.6)	41	(18.4)	122	(85.5)	19	(14.5)		

TABLE 3

tionable whether the streptomycin material should be compared with the "total" PAS material or the "selected" However to exclude too many interfering undefined factors from the PAS material, the "selected" has been chosen for the comparison In order to compare it with the streptomycin material it was necessary to rearrange the material according to the American classifications However, some of the grouping differed too much in the two materials to allow a direct comparison and the evaluation of the treatments have to be described for each material

When reviewing the two *clinical materials* (Table 1) it is astonishing to find that they are comparable in many respects age of patients, character of the pulmonary processes, frequency of cavities and so on The observation time before treatment is two months in both materials The impression has, however, been gained that the cases in the "far advanced" group in the PAS material are more severe than in the streptomycin material This is evidenced by the high frequency of complicating localizations of tuberculosis—especially that of intestinal tuberculosis (Table 2) Thus there should not be expected as good results in the PAS material as in the streptomycin material

The treatment with streptomycin was fixed to four months whereas the PAS treatment was adjusted according to the individual cases As seen from Table 3 the PAS treatment was three to six months in 49 per cent—thus of a similar duration as in the streptomycin material In 30 per cent the PAS treatment was one to three months and in 21 per cent more than six months

In spite of the differences in the duration of the treatment the comparison of the efficacy of the two drugs seems justified, as the majority of the cases in the streptomycin material—about 80 per cent—had developed resistance to the drug within three to four months treatment Therefore, only in a minor number of the cases further improvement could be expected to take place by continued treatment

In the treatment with PAS the problem of bacillary resistance is of less clinical importance as, to our present experience, it develops in a minor part of the cases, is less pronounced and coming first after three to five months treatment (Lehmann¹¹) Some cases have been treated one to two years without developing resistance However, even in a minor part of this material better results could possibly have been attained, as part of the cases were not adequately treated due to lack of PAS during the first year Summing up, it seems as if the two materials to the same degree will present results indicating what can be achieved by the two drugs

As to the *clinical observations during treatment* the PAS mater-

ial shows better results in *temperature and sedimentation rate* (Table 4)

Normal temperature was attained in 75 per cent with PAS, in 47 per cent with streptomycin. A "decrease" in ESR was observed in 84 per cent with PAS, in 30 per cent to normal values, whereas a "decrease" in the streptomycin material was registered only in

TABLE 4
Clinical Observations During PAS Treatment

	— T E M P E R A T U R E —						— GAIN IN WEIGHT —					
	Afebrile throughout		Decrease to normal		No decrease to normal		Unaffected		1 kg or more for the PAS material			
	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct		
PAS material	53	(25.9)	114	(75)	19	(12.5)	19	(12.5)	127	(61.9)		
Streptomycin material	63	(28.2)	76	(47.5)	41	(25.6)	43	(26.9)	188	(84.3)		

ERYTHROCYTE SEDIMENTATION RATE										
	Normal throughout				Decrease				Unaffected	
	No	Pct			No	Pct			No	Pct
PAS material	10	(4.9)			161	(83.7)			34	(16.3)
Streptomycin material	39	(17.5)			94	(51.1)			90	(48.9)

	— S P U T U M —				— BACILLI IN SPUTUM OR LAVAGE —							
	Not present		Disappearance or decrease		Not present before treatment				Present before treatment			
					Continued negative		Changed positive		Changed negative		Continued positive	
	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct
PAS material	18	(8.8)	132	(70.5)	0	(0)	0	(0)	58	(28.2)	147	(71.8)
Streptomycin material	?	(?)	178	(79.8)	?	(?)	?	(?)	82	(43.0)	108	(57.0)

	X-RAY OBSERVATIONS				PARENCHYMATOUS INFILTRATIONS									
	Complete regression		Marked regression		Moder or slight regr				Unchanged				Progress or new infiltr	
	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct		
PAS material	0	(0)	73	(35.5)	60	(29.3)	56	(27.3)	16	(7.8)				
Streptomycin material	6	(2.8)	123	(56.9)	54	(25.0)	14	(6.5)	19	(8.8)				

	X-RAY OBSERVATIONS CAVITIES									
	Closed or lost to view		Smaller		Unchanged		Larger or develop during treatment			
	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct
PAS material	31	(18.3)	46	(27.2)	80	(47.3)	12	(7.2)		
Streptomycin material	47	(25.8)	67	(36.8)	68	(37.4)	0	(0)		

51 per cent The *gain in weight* was superior in the streptomycin material, 84 per cent compared with 62 per cent for PAS However, it is not mentioned how large the gain in weight should be in the streptomycin material to be registered In the PAS material it was at least one kg

Concerning observations in *sputum decrease* and *sputum conversion* the streptomycin material is superior Sputum decrease was observed in 79 per cent as compared with 70 per cent for PAS Still more striking is the difference in sputum conversion 43 per cent and 28 per cent respectively However, here the frequency of the severe cases in the PAS material with old cavities and processes of proliferative type has to be considered In the less severe "total" PAS material the conversion of sputum was 43 per cent To some part these better results in the streptomycin material are assumingly due to the use of collapse therapy in this material

Regressions of *parenchymatous infiltrations* and *cavities* are difficult to compare in the two materials as the figures for the streptomycin material only refers to lesions of the exudative type whereas the PAS material refers to both lesions of exudative and proliferative nature and these were of about the same frequency Even the classifications of the regressions were different in the two materials More comparable is the frequency of "progressions or new lesions" during treatment and this is 7.8 per cent for PAS and 8.8 per cent for streptomycin When studying the streptomycin paper and comparing the different reports with the PAS material it seems, however, as if streptomycin gives somewhat faster and more complete regressions of the infiltrations than PAS Further studies on more comparable materials, or with more comparable registrations, are necessary for definite conclusions

Concerning changes in cavities in the two groups there are not too marked differences "Closure or lost to view" dominates with 23.8 per cent in the streptomycin material as compared with 18.3 per cent in the PAS material

TABLE 5

After Treatment Observations Observation Time 3 Months or More

	Improvement continued		Improvement stationary		Worse		Dead during treat or after observ time	
	No	Pct	No	Pct	No	Pct	No	Pct
PAS material	30	(57.6)	7	(13.5)	7	(13.5)	8	(15.4)
Streptomycin material	77	(34.5)	86	(38.5)	32	(16.4)	2	(2)



FIGURE 1

FIGURE 2

FIGURE 3

Fig 1 A man of 62 years Onset of disease November 1948 Fever, sedimentation rate 50mm/one hour/Westergren, sputum positive, weight 66 kg X-ray just before treatment December 27, 1948 Right hilus enlarged with a walnut sized ring formed shadow Scattered infiltrations of the lung field with another walnut sized thin walled ring shadow medial at the right of the clavicle—*Fig 2* The same case on January 28, 1949 after one months treatment with 14 grams PAS granules a day Normal temperature, sedimentation rate, 6 mm/one hour Clearing of the infiltrative lesions in the lung field and of the walls of the cavities Shrinking of cavities—*Fig 3* Same on June 28, 1949 after continued PAS therapy for six months Cavities lost to view and lung fields nearly cleared of infiltrations Sputum negative on guinea pig inoculation Left hospital June 30, 1949 with a gain in weight of 10 kg

As an illustration of the changes seen on the x-ray films, two cases should be mentioned (See Figures 1-6)

In the *after-treatment observations* (Table 5) the PAS material predominates with a much higher frequency of *continued improvement*—the figures are 58 per cent to 35 per cent for streptomycin. This could possibly be expected as the majority of the bacilli during the streptomycin treatment develop resistance to the drug, whereas this is not the case with PAS. Naturally differences in the judgment of the cases can be responsible to some extent for the different figures.

As to the *deaths*, the frequency in the PAS material is 15.5 per cent. In the single reports on the streptomycin treatment deaths are mentioned, but the total is not given in the leading article.

Recently Bachman, Birath, Karth, Lemming, Lindgren and Lundquist presented another team work on pulmonary tuberculosis.¹²

When comparing PAS and streptomycin attention has to be paid to other properties of the two drugs which have not been registered in the tables, and these are

- 1) The frequency with which drug resistance is developed during treatment
- 2) The mode of administration, and
- 3) The toxicity of the drugs

The daily intramuscular injections of streptomycin is a drawback for this treatment and still more this is the case with the toxic reactions involving the nervous system, which restricts the use of streptomycin in minimal lesions, thus just in those phases of the disease, in which a chemotherapeutic agent has the greatest possibilities. There was a high frequency of drug resistance in the treatment with streptomycin—in 80 per cent of the cases the bacilli were found resistant after three months treatment. With PAS we have only found a slight resistance in a minor part of the cases and it is developed only after several months of treatment.

As a *general conclusion* of this comparison between the two drugs, it must be said that their effect on the symptoms are somewhat different, the streptomycin appearing to dominate in the x-ray findings whereas PAS dominates in its effects on temperature and sedimentation rate and seems to give more stable after-treatment results. The lack of toxemic reactions when using PAS as compared with streptomycin is to the benefit of the former drug and allows us for the first time to treat even early and slight cases of all forms of tuberculosis chemotherapeutically, possibly even out-door patients.

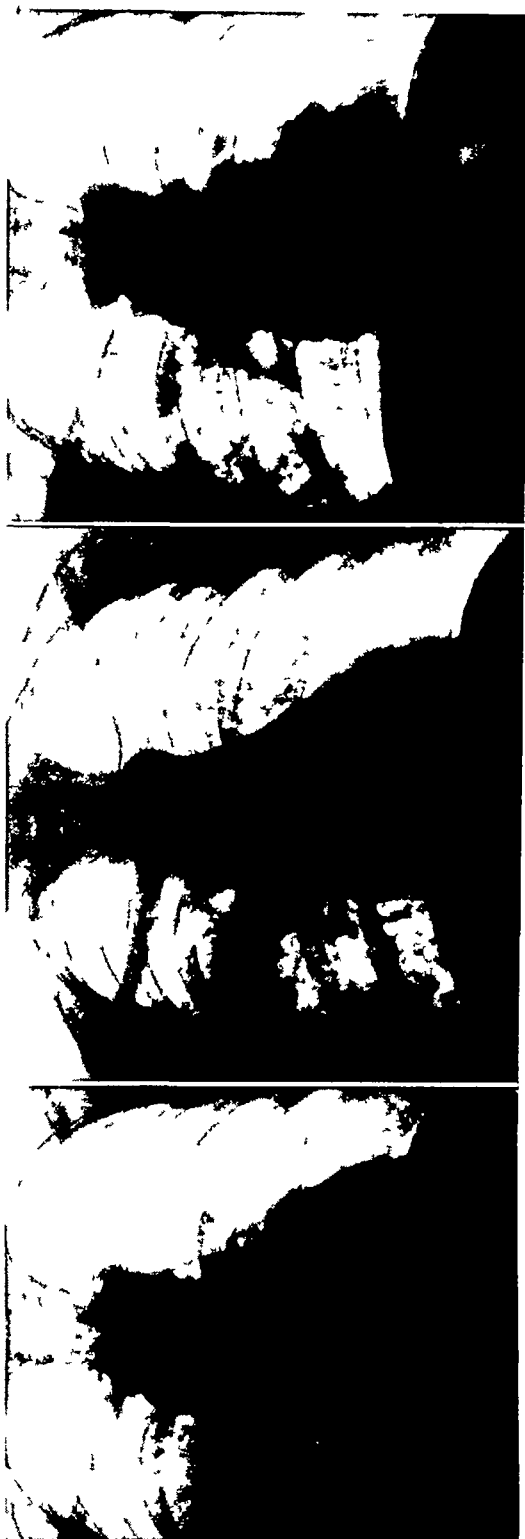


FIGURE 4

Fig 4 A woman of 24 years Acute onset of disease June 1944, ordinary sanatorium regime to November 1945 when she had an acute spread in the right lung with high fever, sputum positive (slide) X-ray November 13, 1945 before treatment Diffuse infiltration of the right middle and lower part of the lung PAS instituted November 15 in a dose of 14 grams PAS granules a day and continued to March 27, 1946 —*Fig 5* The same case on December 12, 1945 Afebrile X-ray shows considerable clearing of the lung field especially the lower part —*Fig 6* The same on March 19, 1946 Continued clearing of the infiltrations in the middle part of the lung Sputum still positive (guinea pig) In May she had a relapse on the right side with a cavity of walnut size She responded favorably on retreatment with PAS and left the hospital February 4, 1949, sputum negative, and has since had no relapse

FIGURE 5

FIGURE 6

Tracheo-bronchial Tuberculosis

At several meetings of the Swedish Tuberculosis Association during the past years cases of tracheo-bronchial tuberculosis—including laryngitis—treated with PAS have been presented Carstensen especially has stressed the striking effect of PAS in these cases and in all forms of tuberculosis in the mucous membranes Vallentin has also reported more cases with a good effect von Rosen has compared streptomycin with PAS treatment using aerosols and has seen good effect of streptomycin but no effect of PAS The failing effect of PAS in aerosols could be anticipated as it is absorbed too quickly from the mucous membranes to produce any therapeutic effect even if given three times a day as inhalations during 15 minutes

Intestinal Tuberculosis

The most dramatic effects of PAS in the treatment of tuberculosis has been achieved in cases of intestinal tuberculosis as reported by Carstensen and Sjölin¹³ The material consisted of 22 cases of pulmonary tuberculosis complicated with intestinal localizations, verified by x-ray in 21 cases and postmortem in the 22nd Twenty of the 22 cases had exudative cavernous pulmonary lesions, all with bacilli in sputum In the other two cases the pulmonary process was predominantly of a nodose type and rather stationary Most of the patients (20) had abdominal pains continuously, tenderness in the right iliac fossa and diarrhea, high temperature and sedimentation rate All patients were seriously ill and the prognosis considered doubtful or unfavorable—in some cases hopeless

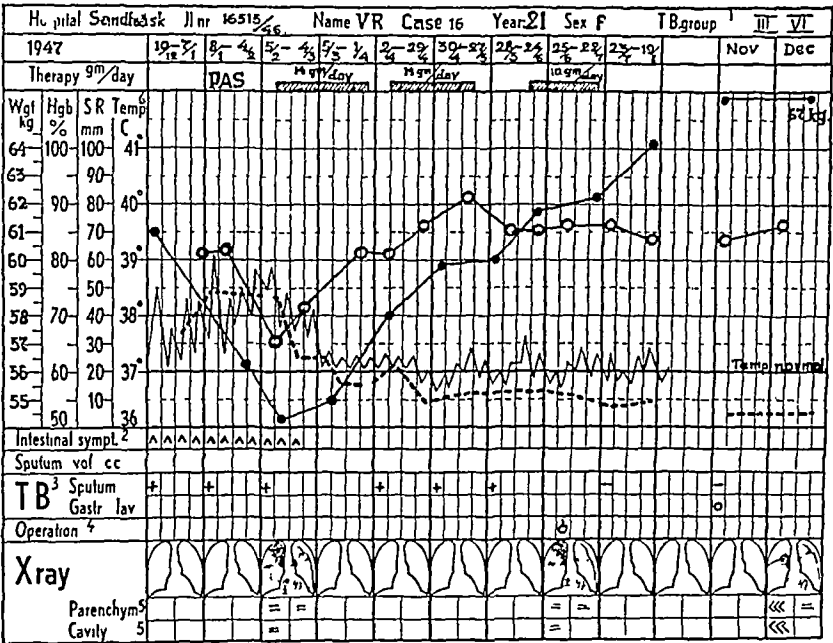
Before the PAS treatment the patients had been hospitalized for five to seven months and all forms of treatment tried without success

The *treatment with PAS* was continued for three to 15 months and was often started over again in connection with performed operations PAS was given in periods of three to six weeks with free intervals of about a week The dosage varied from 6 to 14 grams PAS granules a day and was given by mouth in four to six doses A dosage of 14 grams was generally used but in some cases not tolerated and the treatment therefore often commenced with a lower dose (6, 8 or 10 gms)

The *effect of the treatment* was in the most striking way evidenced by the improvement of the *intestinal symptoms* All the patients were nearly or completely freed from their abdominal complaints within two to four weeks The severe diarrhea, refractory against constipating drugs, ceased and so did the often unbearable pains After-treatment barium enemas showed roent-

genographic improvement in five cases out of the examined 11 patients with total regression in two In one case with fatal issue the necropsy proved that the intestinal process was in a healing phase

The effect of PAS on the *general condition, temperature, sedimentation rate and weight* was in several cases even more pronounced than in cases of pulmonary tuberculosis In 15 the weight increased 1 to 23 kg , simultaneously with the general well-being In seven cases it remained unchanged or decreased The temperature became normal in 15 out of the 19 patients who were afebrile, while the other four showed only initial or incomplete fall of the temperature In 11 cases the sedimentation rate became normal In cases, where the temperature and sedimentation rate remained high, far advanced and progressive lesions of the lungs were present There was a rather rapid increase in the hemoglobin, when low before treatment



1 Imening IImlar IIIpalm. exs IVpalm. prod Vlar bronch VIintest VIIurogen VIIIbone joint IXpleurit emp perit. abs. fist
2 Vomiting v Diarrhea. ^ 3 Slide pos + neg + Culture pos ● neg ○ Animal pos. ▲ neg △
4 Pneumoth ○ Th centhes ● Th caustic. ◐ Th plastic. ■ Phren crush x Pneumo perit. ○
5 Progression > to >>> Regression < to <<< Status quo = 6 Temp — SR - - Hgb% ○-○-○ Weight ●-●-●
6 Temp — average a week

FIGURE 7 Case of pulmonary tuberculosis complicated with intestinal tuberculosis Observe the high fever during nine weeks before treatment accompanied with a sharp drop in body weight and hemoglobin After the institution of PAS the fever decreased and is nearly normal after three weeks and the sedimentation rate follows the drop in temperature down to normal values The diarrheas disappear after two to three weeks treatment and the body weight and hemoglobin respond with a dramatic increase After Carstensen and Sjolvin

As to the *pulmonary lesions* there was observed roentgenographic regressions in eight cases having fresh exudative processes. In two it was possible to institute pneumothorax and five have undergone successful thoracoplasties.

Of the 22 cases treated, 19 improved, three became worse, and one of them died.

In order to visualize the changes during treatment one of Carsensens and Sjolins cases should be mentioned—a female, born 1926.

Pulmonary tuberculosis was diagnosed in November 1944: exudative cloudy lesions in the left middle lobe and fibrotic, nodose processes all over the right upper lobe. Thereafter the patient was treated at several sanatoria and admitted to Sandtrask in July 1945. Left pneumothorax was instituted in December 1945. Thereafter the lung lesion remained on the whole unchanged until November 1946, when some progress with a small cavity in the right apex was observed. Since November 1946 also abdominal symptoms with pains, diarrhoea, tenderness in the cecal region, high, remittent temperature (the patient was previously afebrile), loss of weight, high sedimentation rate. *Barium enema in February 1947*. Pronounced changes in the cecal region. *PAS treatment was started on February 10, 1947*. There was immediate improvement and the abdominal symptoms completely stopped after 10 to 14 days, the general condition quickly improved (Fig. 7). The lung lesion remained on the whole unchanged with the small right apical cavity and bacilli in the sputum. Right pneumothorax was instituted on July 9 with good results. After pneumothorax the sputum converted to negative. *Barium enema on October 3, 1947* showed marked regression. The patient was discharged from the sanatorium in January 1948. She was in an excellent condition, had no symptom and was able to start work.

Another similar investigation on about 20 cases of intestinal tuberculosis was presented at the Nordiske Tuberkulose lagekongress in Helsingfors, 1949 by Kallquist¹⁴. The results were in full agreement with the above mentioned.

Encephalo-meningeal Tuberculosis

The experience in the treatment of these forms of tuberculosis with PAS is rather limited because of their low frequency in Sweden. The writer has treated six cases, none of them living after one year. There is generally seen initial improvement and the patients have been kept alive for weeks or months. In a few cases death suddenly occurred during improvement, assumingly due to hydrocephalus internus, the presence of which was verified by necropsy. Microscopic examination showed that the processes in the brain and the meningeas were in a healing phase with fibrotic involvement of the aqueductus leading to the hydrocephalus.

PAS was in the first cases given as a permanent intravenous 2 per cent infusion with a total dose of 20 to 30 gm PAS in 24 hours. However, thrombophlebitis occurred regularly after three

to five days. In other cases peroral administration of the sodium salt-enteric coated in small granules—was used in the same dosage. Intestinal complaint (diarrhea) developed after using 30 grams per 24 hours. In two cases a 2 per cent PAS solution was given by duodenal tube instead of intravenously and high blood concentrations (20 to 25 mg per cent) were found with values of 10 to 12 mg per cent in the cerebrospinal fluid. Usually the concentration in the cerebrospinal fluid is one-third to one-fourth of the blood concentration. Therefore the unsatisfactory results in the treatment of encephalo-meningeal tuberculosis is not due to unsatisfactory penetration of the cerebrospinal barrier but rather to a low solubility of PAS in the brain tissue. Treatment of this disease with PAS alone can thus not be recommended. Combined therapy with shorter periods of streptomycin treatment together with permanent PAS therapy has been successful (Carstensen and Soderhjelm¹⁵).

Miliary Tuberculosis

Miliary tuberculosis has reacted better on PAS treatment than encephalo-meningitis. In the mentioned team work on pulmonary tuberculosis four cases of miliary tuberculosis (from Renströms Hospital) were included. In the Childrens Hospital in Gothenburg a few cases have been successfully treated (Y Akerrhen and the writer) without relapses after one to one and one-half years. A detailed description of these cases has not yet been published. Combined therapy with streptomycin has been more successful than PAS or streptomycin alone (Carstensen and Soderhjelm).

Tuberculosis of the Kidney and Urinary Tract

About 60 cases of urogenital tuberculosis have been treated by E Ljunggren and O Obrant at Sahlgrens Hospital in Gothenburg and at the Ravlanda sanatorium, connected to the hospital as a specialized ward for these cases and in charge of Dr Ljunggren. Preliminary reports on kidney tuberculosis (Ljunggren¹⁶) have been presented, from which the following data are collected. In many of the cases combined chemotherapy with PAS, calciferol, streptomycin, chaumogra oil or TB I has been used. As these cases are unsuitable for elucidating the therapeutic effect of PAS they are not mentioned here. In other cases the treatment could not be continued for a sufficient length of time due to social or economical factors. Therefore, only cases being under the treatment, ward and observation for more than one year will be mentioned.

None of the cases had active pulmonary tuberculosis. The examination of the patients included analysis of the urine for tubercle bacilli (culture and guinea pig tests) once a month and in men

even examination of seminal fluid or prostate secretion if negative in the urine, non-protein nitrogen, urine cast and urea clearance. Intravenous pyelogram and, if not considered dangerous, cystoscopy was undertaken. The patients were afebrile and had normal or slightly elevated sedimentation rate. Three cases of *bilateral* kidney tuberculosis should be mentioned.

The first was a woman, aged 32, with painful cystitis and several small ulcers in the bladder. The pyelogram showed bilateral changes in the upper and lower calyces. She was treated with PAS in a dose of 8 to 10 grams PAS granules a day for 14 months altogether with a few free intervals of one to two months. The pains from the cystitis improved rather soon during the treatment and after three to four months they had disappeared together with the ulcers in the bladder. After seven months there was conversion in the urine and the guinea pig test has been negative for 18 months (more than 10 examinations). The processes in the calyces have shown signs of healing—partly with calcification—on the x-ray films.

The second case was a woman of 48 years. The pyelogram showed processes in both kidneys but there was no cystitis. She was treated for 14 months without interruption with eight grams PAS granules a day (equal to 6 grams PAS). The guinea pig test was positive once during the first week of treatment. Seven consecutive tests during the following year were negative.

The third case was a man of 35 years, with complicating genital tuberculosis. In one kidney two small calcifications were seen. The urine from this kidney was positive in guinea pig inoculation. The other kidney showed an abnormal pyelogram. After eight months treatment with eight grams PAS granules a day he converted in the urine and has since been negative (14 months with eight guinea pig tests).

Two cases of *unilateral* tuberculosis have been under observation for more than one year. Both of them had kidney and genitrary tuberculosis. One of the cases was not operated upon because of chronic nephritis with improper kidney function test. He was treated for six months with PAS in a dose of eight grams granules increasing to 12 grams a day without conversion in the urine. Combined therapy with chaumogra oil and streptomycin resulted in conversion within a month. The role played by PAS in this case is not easy to evaluate. Possibly the patient had converted with PAS alone as more cases did so after seven to eight months treatment.

The other case was not operated upon because the kidney process was of a type where chemotherapy alone was considered prosperous. This suggestion was verified by conversion in the urine after two months treatment with 8 to 10 grams PAS granules a day and more negative tests during six months.

Of five cases with tuberculosis in the *remaining kidney after*

nephrectomy one case had positive guinea pig test after 11 months treatment with 10 grams PAS granules a day, a hopeless case with only a minor part of the kidney intact and complicated with genital tuberculosis. His cystitis improved however and he was freed from symptoms after two to three months treatment. Another case did not convert after seven months on 8 to 12 grams PAS granules, but he is nearly free from cystitis. A third case with a minor cavity in the kidney and genital tuberculosis converted after eight months on 8 to 10 grams PAS granules and symptoms of cystitis disappeared after two months treatment. He has remained negative for five months. The remaining two cases have been treated too short a time to be mentioned here.

Recently Linden,¹⁷ at the annual meeting of the Swedish Surgical Association in 1948, demonstrated a case of primary renal tuberculosis which had been treated with PAS for six months prior to the nephrectomy and in which the tuberculous process was in a healing stage. Linden, therefore, considered that it would have been better in this case if nephrectomy had not been carried out. Odelberg,¹⁸ on the same occasion, reported a case in which cystitis, pyuria and tubercle bacilli in the urine occurred six months after nephrectomy for renal tuberculosis. A tuberculous lesion was seen in the kidney (destruction of the upper calyx) and a large tuberculous ulcer of the bladder was also found. After two and one-half months treatment with PAS the patient became free from symptoms, the pyuria had disappeared and the ulcer in the bladder had healed, the change in the calyx however, remained.

Summing up the results it can be said that PAS in nearly all cases has given amelioration of the cystitis and rendered the majority free from symptoms. Ulcers in the bladder have healed. Conversion in the urine has been seen in more cases within eight months treatment and remained negative (6 to 12 months observation time). No case has shown progression on the x-ray during the treatment. A higher dosage of PAS than here used may give better results.

Skin Tuberculosis

Lemming¹⁰ in 1948, reported a case of chronic skin tuberculosis (history 10 years) in which healing of a hand flat sized ulcer on one foot occurred after six weeks local treatment with a 10 per cent PAS solution. This was applied with a gauze wetted in the solution and changed several times a day. There was a relapse soon after the healing but retreatment healed the ulcer again and it has remained so after observation for more than one year.

Carstensen recently presented three cases of lupus vulgaris also treated locally with PAS with good result. One of them was treated

with Finsen light and vitamin D without success. The ulcerations around her nose prohibited her from living among other people. The disease healed on PAS within six months.

Other Forms of Tuberculosis

Little experience has been reported on the effect of PAS on other forms of tuberculosis as orthopedic and sinus tuberculosis and lymphadenitis. Orthopedic cases seem to react slowly or not at all on peroral treatment, possibly better if local treatment can be applied. Two cases of otitis have healed on peroral PAS (Smars and Kempe¹⁹). Cases of tuberculous peritonitis and salpingitis have also responded favorably on peroral PAS treatment.

Surgical Prophylaxis

From a theoretical point of view PAS should be well adapted for protection in operations as resistance to PAS is not generally developed during treatment and coming late if at all. The few reports on its use pre and postoperatively are encouraging. Odelberg²⁰ and Bruce and co-workers²¹ have this year presented papers on the subject which will soon be published.

Combined Chemotherapy

In the above presentation the use of PAS combined with other chemotherapeutics has not been mentioned. The reason for this is that representative and conclusive series have not yet been published. However, PAS combined with sulfa drugs or penicillin was early used by Vallentin in the local treatment of empyema with mixed infections and especially by Westergren and co-workers²² in pulmonary tuberculosis (peroral or parenteral). Westergren has stressed the beneficial effect of changing from one drug to another, using PAS, streptomycin, penicillin and different sulfa drugs or a few of them together. He also observed a delayed or diminished emergence of resistance to streptomycin when PAS was simultaneously given. Carstensen and co-workers have, as mentioned above, used PAS continuously with shorter periods of streptomycin in military and encephalo-meningeal tuberculosis. Recently Kristensson²³ presented a series of far advanced and hopeless cases of pulmonary tuberculosis with multiple cavities. With combined PAS, streptomycin and penicillin given continuously all together a dramatic effect was achieved in the majority of the cases.

Ambulatory Treatment

The absence of real toxic side effects of PAS and the peroral use invites to the ambulatory use of the drug under controlled conditions. In Stockholm Bluhm²⁴ has started the ambulatory

treatment in a small series from his dispensary station and presented preliminary results. In Gothenburg a similar study is going on.

When reviewing the work on PAS during the five years it has been available to use in the clinic, it must be emphasized, that the experience in many respects is rather restricted. This is partly due to the limited supplies available during the first two years and partly to the high price. Difficulties in overcoming the intestinal complaints connected to the acid character of PAS has been a third limiting factor. As the new synthesis of PAS from meta-amino-phenol simplifies the production, the supplies should be sufficient and the price acceptable. Whether PAS should be used routinely as an acid-enteric coated, or as the sodium salt, is still a question to be answered.

The optimal dose of PAS for the different forms of tuberculosis has not been satisfactory elucidated. That the highest doses (20 to 30 grams Na-PAS) should be used in cases of miliary and encephalo-meningeal tuberculosis seems justified and that lower doses than 11 to 12 grams PAS (14 grams granules) a day can be used in kidney-urinary tuberculosis due to the high concentrations in the urine. For most of the other forms of tuberculosis a dose of 10 to 12 grams PAS giving blood concentrations of two to six mg per cent seems reasonable.

That PAS should be given *continuously*, if possible, has been illustrated by the increase in sedimentation rate and sometimes even in temperature when it has been stopped for a week or two. The length of the treatment should be determined for each case but it should be kept in mind, that even if amelioration in the general condition, the decrease in temperature and sedimentation rate are appearing early, the regressions of the lesions, at least in the lungs, are slower and the most demonstrable changes occurring between the third and sixth month. The treatment should naturally be continued as long as improvement is seen and usually the end state should be stabilized by another months treatment.

Recent investigations in vitro, in animal experiments and in the clinic seems to indicate that the combined therapy with PAS and streptomycin will give results superior to those with each drug alone. Beside that, the combined therapy has another perhaps still more remarkable feature, the depression or delay of the emergence of resistance to the drugs. This does mean that the duration of the treatment can be prolonged and perhaps widen the indication for their use.

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Selecting the Streptomycin Regimen for Patients with Pulmonary Tuberculosis with Special Reference to the Intermittent Dosage Schedule*

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Streptomycin research in the treatment of patients with pulmonary tuberculosis has passed through a number of stages, and in the course of these investigations, an attempt has been made to answer the following questions

- 1) Is streptomycin effective in the treatment of pulmonary tuberculosis?
- 2) In which phase of tuberculosis is streptomycin most useful?
- 3) How can we overcome the toxicity factor?
- 4) How can we reduce the incidence of, or avoid the loss of bacterial sensitivity to streptomycin?
- 5) Which type of regimen should be used for the various types of cases?

Numerous investigators have substantially answered the first three questions 1) that streptomycin is effective in the treatment of pulmonary tuberculosis, 2) that it is most effective in the treatment of recent exudative lesions, and 3) that toxicity can almost be eliminated by reduction in the dosage and length of time the drug is administered. In this preliminary report, we are attempting to summarize recent developments pertaining to the remaining two closely associated problems, namely, 4) the reduction of "bacterial resistance" to streptomycin, and 5) the type of streptomycin regimen to use.

The matter of "bacterial resistance" to streptomycin should receive first consideration, because if we render the use of this remarkable chemotherapeutic agent impossible by improper administration, we are wasting one of the most important weapons we possess in the treatment of pulmonary tuberculosis. To properly evaluate this factor, careful bacteriological studies were conducted on various streptomycin regimens at Fitzsimons General Hospital (Chart 1). It was demonstrated by this work that the shorter

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CHART 1

The Incidence of Streptomycin Resistant Tubercle Bacilli Developing During the Treatment of Pulmonary Tuberculosis by Various Dosage Schedules

(a) Comparison of All Schedules (SM given intramuscularly)

Regimen Number	Daily Dosage Schedules	No of Cases (Total 408)	Percentage Resistant*			
			Days after Beginning of Therapy			
			30	60	90	120
1	2 gm, 120 days	100	0	23	46	72
2	1 gm, 120 days	37	0	18	45	67
3	1 gm, 42 days	21	0	25	25	25
4	1 gm, 28 days	67	0	8	6	5
5	½ gm, 28 days	28	0	0	0	0
6	1 gm, 28 days, repeated after 6 weeks, a total of 56 gms in 98 days	35	0	0	13	30

Intermittent Schedules

7	1 gm q 3 days, 120 days	50	0	24	17	34	
8	2 gm q 3 days, 120 days	50	0	62	20	32	
9	2 gm DHSM** q 3 days, 30 days	20	0	0	0	0	

*Definition of bacterial resistance Cultures with growth comparable to the control (0 mcg/ml) on Herrold's egg-yolk agar containing 10 mcg of streptomycin per ml

**Dihydrostreptomycin

(b) The Intermittent Schedule (Regimens 7 and 8 above)

Therapeutic application based upon a consideration of the "resistance factor"

Days of Treatment	Per cent Resistant Cases*	Treatment
0	0	Short courses (30-60 days) of intermittent streptomycin Rx are satisfactory for most cases of pulmonary tuberculosis with recent exudative lesions. They may be <i>definitive</i> with rest, or <i>adjunctive</i> for operations, particularly temporary collapse. Other uses include <i>symptomatic</i> treatment and as a <i>therapeutic trial</i> . NOTE LOW INCIDENCE OF RESISTANT CASES (3.9 per cent at 60 days)
30	0	
42	0	
60	3.9	
70	4.2	Long courses (60-120 days) of intermittent streptomycin treatment are better and often required in the treatment of caseous pneumonic tuberculosis (particularly acute lobular or lobar pneumonia). Its greatest usefulness in these cases is as an <i>adjunct</i> to prepare the patient for temporary collapse or surgical procedures. NOTE PROGRESSIVE INCREASE OF RESISTANCE FROM 70th TO THE 120th DAYS
80	8	
90	18	
100	24	
110	31	
120	33	

*Studies made by the Laboratory Service, Fitzsimons General Hospital, Denver, Colorado, on one hundred (100) cases averaging three (3) cultures weekly per patient

CHART 2

Planning Definitive Treatment for Pulmonary Tuberculosis
Based on Clinical Pathological Types

CLASSIFICATION OF PULMONARY LESIONS Based on progress studies—x-ray, laboratory and clinical findings DESCRIPTIVE TERMS USED IN CLASSIFICATION APPLY TO X-RAY FINDINGS		MED RX		SURG RX	
		SM Regime	Tem Col	Per Col	Exc Sur
UNCLASSIFIED					
New patients—evaluation incomplete)	1				
NEW SOFT LESIONS					
Resolving type—good resolution (exudative)	2	Short	×		
Non-resolving—poor resolution (caseous)	3	Long	×		
Mixed (exudative and caseous)	4	Long	×		
OLD HARD LESIONS					
Cavitary (fibrocaseous cavernous)	5			×	
Localized (tuberculoma)	6	Pro			×
OLD AND NEW MIXED LESIONS					
New Component	7	S/L	×		
Old Component	8			×	×
MILIARY TUBERCULOSIS	9	Special			
APPARENTLY CURED (NTA Standards)	10				

KEY SM—Streptomycin regimen Short course (30-60 days, SM daily or q 3 days), Long course (60-120 days, SM daily or q 3 days), Pro—prophylactic (1 week before, 2 weeks postoperatively), S/L—Short or Long course, as indicated, Special—Special course (Long or Short courses of SM alternating with PAS)
 ×—Operations often required for definitive treatment
 TEM COL—Temporary collapse (pneumothorax or pneumoperitoneum)
 PER COL—Permanent collapse (extra pleural thoracoplasty)
 EXC SUR—Excisional surgery (segmental resection, lobectomy and pneumonectomy)

NOTE A strict rest regime is an essential part of the management

GENERAL PRINCIPLES OF THERAPY ILLUSTRATED IN THE CHART
(See Classification Number above)

(Great individualization is required in applying treatment and the principles summarized below are meant only to illustrate a broad viewpoint required in planning therapy The conclusions on streptomycin are tentative, and based on current research)

- 1) *Unclassified* The new patient falls in this group on admission to the hospital unless classified by previous clinical studies, serial x-ray examination or strong clinical evidence As the clinical picture clarifies, the patient usually falls in one of the classifications below for treatment
- 2) *New Soft Resolving Lesions—Good Resolution (Exudative)* Rest alone may prove to be definitive treatment With unfavorable trend, persistent toxemia, positive sputum and/or cavitation, the plan of treatment should include streptomycin (Short regimen, 30-60 days, daily or intermittent schedules) and temporary collapse
- 3) *New Soft Non-Resolving Lesions—Poor Resolution (Caseous)* As for

Number 2, except that extensive disease, particularly acute caseous pneumonia, constitutes a medical emergency and a Long course of streptomycin (60-120 days, preferably the intermittent regimen) is indicated. The fibrocaseous cavernous residuals must be treated as old hard lesions (see Numbers 5 and 6) after an appropriate period of stabilization by medical management.

- 4) *Mixed New Soft Resolving and Non-Resolving Lesions* As described for Numbers 2 and 3
 - 5) *Old Cavitory Lesions (Fibrocaseous Cavernous)* Permanent collapse is usually required for persistent cavitory lesions, but some cases require excisional surgery when the type and location of the lesion make collapse therapy ineffective. Streptomycin is not advised except for "spreads" after thoracoplasty, or prophylactically for resection.
 - 6) *Old Hard Localized Lesions (Tuberculoma)* Excisional surgery required. Short prophylactic course of streptomycin usually indicated (one week before, two weeks after operation).
 - 7) *Old and New Mixed Lesions—The New Component* is usually given first attention. A short or long course of streptomycin, with or without temporary collapse, is prescribed as required.
 - 8) *Old and New Mixed Lesions—The Old Component* may be controlled by the measures prescribed for the new lesions, if not, treatment must be surgical (see Numbers 5 or 6).
 - 9) *Miliary* Special long courses of streptomycin are required. This includes combinations of streptomycin and para-aminosalicylic acid (PAS) and/or alternating months of therapy with these agents.
 - 10) *Apparently Cured (NTA Standards)* No treatment. Periodic examinations (x-ray, etc.) are required.
-

the course of streptomycin and/or the smaller the daily dosage, the lower the incidence of "bacterial resistance." As compared with daily dosage schedules of similar lengths, the interrupted streptomycin schedules (streptomycin injected intramuscularly every third day) resulted in a marked delay in the emergence of resistant strains of tubercle bacilli. Other factors (cavitation, etc.) contribute to the early development of resistant strains of organisms, but when the drug is really needed, consideration of the method of administration is of paramount importance, as this factor lies within our control.

Keeping in mind the resistance studies just reviewed, consideration can now be given to other factors which influence the decision on the type of regimen to be selected for treating patients with pulmonary tuberculosis. First of all, it is of primary importance that certain principles of therapy based upon an evaluation of the pathological types of lesions be carefully reviewed before streptomycin is prescribed. Moreover, the place of this chemotherapeutic agent in the definitive treatment of pulmonary tuberculosis is largely determined by this factor, and a reasonable attempt must be made to classify the pulmonary lesions, if treatment is to be placed on a rational basis (Chart 2). It must be determined whether or not there is a new lesion which will respond to conservative measures of therapy, or an old lesion which will require a radical approach. Every effort must be made to make this and similar decisions if treatment is to be instituted promptly, effectively and safely.

CHART 3

THE PLACE OF SM IN THE PLAN OF TREATMENT
OF PULMONARY TUBERCULOSIS

The indication for the use of Streptomycin (SM) should be clearly defined at the time it is prescribed, and *there should be a real need for its use*

I **DEFINITIVE WITH REST TREATMENT** (Rx) (Streptomycin expected to give favorable result—arrested disease or apparent cure—without resort to other measures)

- 1 New soft lesions (exudative, etc)
- 2 Some few cases of acute tuberculous pneumonia (treated early emergency)
- 3 Progressive primary tuberculosis (pulmonary and glandular lesions)
- 4 Miliary tuberculosis
- 5 Treatment for recent reactivation or spread in old cases
- 6 Post-hemoptoic spreads
- 7 Tuberculous complications preventing good pulmonary response to rest (bronchial, etc)

(Some of above may fail to respond to streptomycin and fall in other groups below)

II **ADJUNCTIVE TO OPERATIVE PROCEDURES OF ALL TYPES**

- 1 *Preparation* for operative procedures (streptomycin used to improve operability)
 - a Lesions potentially suitable for temp coll (predom exudative, recent cavitation, etc , in which SM is used to reduce danger of complications)
 - (1) To promote resolution and reduce symptoms (toxemia, sputum, etc)
 - (2) For endobronchial disease (reduce danger of tension cavities, atelectasis and/or blocked drainage)
 - b Acute and chronic caseous pneumonic cavitary tuberculosis
 - (1) If lesions are not extensive, SM may prepare for temporary collapse
 - (2) SM usually used to reduce inflammatory phase prior to permanent coll
 - c Operable advanced bilateral disease
 - (1) Unilateral permanent collapse (worse side)
 - (a) Opposite side controlled by streptomycin
 - (b) Opposite side controlled by streptomycin and temporary collapse
 - (2) Bilateral permanent collapse
 - (a) Both sides prepared by streptomycin
 - d Inoperable cases (use of streptomycin in attempt to convert to reasonable risk for surgery)
 - (1) Successful conversion
 - (2) Unsuccessful conversion (continue other Rx with or without SM)
 - (a) Proceed with surgery if delay courts disaster
 - (b) Continue conventional therapy for better risk
- 2 *Prophylaxis* (Protection during and after operative procedures)
 - a Prevention of spreads during thoracoplasty for recent disease
 - b Prevention of empyema and fistula after excisional surgery
- 3 Rx objective altered by unpredicted response to SM, combined uses of SM
 - a "Definitive Rx" changed to "Adjunctive" if operation becomes necessary
 - b "Adjunctive Rx" changed to "Definitive" if result warrants (unusual)
 - c "Symptomatic Rx" changed to "Adjunctive"—operation made feasible by unexpected response to streptomycin
 - d Continuation of streptomycin for prophylaxis after use in "preparation "
- 4 Other adjunctive uses

- a Post-op reactivation or spreads (post-thoracoplasty, etc.)
- b Tuberculous complications preventing good pulmonary response (bronchial, etc.)

III *SYMPTOMATIC TREATMENT* (Relief of distressing symptoms, no expected effect on the pulmonary lesions—far advanced “panic cases” Use cautiously¹)

- 1 Pulmonary complications
 - a Severe painful productive cough, dyspnea, etc
- 2 Non-pulmonary complications (SM may be definitive for local extrapulmonary lesions)
 - a Painful ulcers of the mouth, larynx and respiratory passages
 - b Tuberculous enterocolitis with abdominal discomfort

IV *THERAPEUTIC TRIAL FOR PULMONARY TUBERCULOSIS SUSPECTS* (rarely necessary)

- 1 Serious cases, e.g., miliary suspect lacking bacteriologic proof
 - 2 Serious progressive lesion, tuberculosis suspect, no bacteriologic proof
-

The type of regimen to select in the treatment of pulmonary tuberculosis will be almost as varied as the indications for streptomycin (Chart 3). It is important, therefore, that we clearly indicate the purpose for which streptomycin is being given, and answer certain questions relative to its use. Is it being used for 1) *definitive therapy* in which there is a reasonable chance that an apparent cure will result from the use of the drug (combined with rest therapy) without resorting to operative procedures, 2) as an *adjunct to operative procedures* in which streptomycin is prescribed with a definite feeling that it alone (combined with rest) will not bring about a favorable result, 3) for *symptomatic treatment* in which the drug is expected to relieve severe, distressing symptoms, even though the type of pulmonary disease present is such as to resist treatment, or 4) as a *therapeutic test* in which streptomycin seems indicated for urgent reasons (serious cases such as miliary tuberculosis suspects, etc.)? Viewed in this light, the benefit from streptomycin is measured not so much by its influence on the pulmonary lesion per se, but rather on its contribution to the successful management of the case. This concept is reflected in the present trend of streptomycin research, namely, that of finding the place of streptomycin in the overall plan of treatment of pulmonary tuberculosis.

It is not within the scope of this brief discussion to supply statistical tables on the clinical and x-ray results attributed to the various streptomycin regimens. In research studies made on more than 1500 patients with pulmonary tuberculosis treated with streptomycin at Fitzsimons General Hospital, the results were satisfactory when the kind and length of the treatment schedule was appropriate for the type of problem under observation (Charts 2 and 3). Aside from the long dosage schedules of one or two grams of streptomycin daily for four months, which produced

marked toxic symptoms and resistant organisms in approximately 75 per cent of the cases, there were few serious draw-backs to the regimens (Chart 1) when they were properly prescribed

Difficulties arose in using the short courses of streptomycin therapy, because the lag in x-ray evidence of improvement (resolution) made it difficult to determine the trend of the disease in less than six to eight weeks. An attempt to overcome this handicap was made by using interrupted short courses, that is, one gram of streptomycin daily for 28 days, followed by a six weeks interval without the drug, and finally, a similar 28 day course of streptomycin for those cases in which it appeared to be indicated clinically, roentgenologically and bacteriologically. A small percentage (8 per cent) of the more active lesions (e.g., acute caseous pneumonic cavitory lesions) relapsed during the six weeks interval without chemotherapy. At the 120 day observation point, the percentage of resistant cases rose to 30 per cent. With little reduction in therapeutic efficiency, therefore, this represented a considerable decrease in the number of resistant cases as compared to the 120 day regimens of continuous daily streptomycin therapy. Furthermore, the toxic reactions to the drug as prescribed in this manner, were practically nil. This same principle of therapy was applied successfully to the intermittent streptomycin schedule, using courses of one month and rest periods of one to two months. The number of cases so treated was too small, however, for statistical analysis, but the outlook for such streptomycin regimens appears to be quite promising.

SUMMARY

On the basis of current streptomycin research studies at Fitzsimons General Hospital, certain tentative conclusions regarding the type of streptomycin regimen to select in the treatment of patients with pulmonary tuberculosis seem justified, as follows:

- 1) We should use the shortest course of streptomycin therapy which will accomplish our purpose, in order that we may reduce the number of cases developing "bacterial resistance."

- 2) That *short* courses (30-60 days) of streptomycin are satisfactory for most cases of pulmonary tuberculosis with recent exudative lesions.

- 3) That *long* courses (60-120 days) of streptomycin are better and often required in the treatment of patients with caseous pneumonic tuberculosis (particularly severe acute lobar or lobular pneumonia). In these cases where streptomycin may prove to be life saving, the danger of "bacterial resistance" must be disregarded.

- 4) That *long* courses of treatment or interrupted *short* courses

of streptomycin over a long period of time are required for miliary pulmonary tuberculosis with or without meningitis

5) That the intermittent streptomycin schedule¹ using one or two grams of the drug every third day for one to four months, will give clinical and roentgenological results comparable to those obtained by one or two grams daily dosage schedules over similar periods of time, without significant toxic reactions to the drug. In addition, the important factor of delaying the emergence of streptomycin resistant organisms is proved. In our series, no case with "bacterial resistance" developed in 42 days, only 3.9 per cent at 60 days, 4.2 per cent at 70 days, 8 per cent at 80 days, 18 per cent at 90 days, 24 per cent at 100 days, and 33 per cent at 120 days. In other words, this effective method of using the drug can be utilized for a prolonged period with less danger of encountering "bacterial resistance" than from any of the other regimens reported upon in this study. The intermittent regimen can be used for periods of from one to four months or longer, either continuously or in interrupted short courses, depending upon the purpose for which it is prescribed. Of all courses of streptomycin therapy studied at Fitzsimons General Hospital, it appears to have the greatest utility in the management of all forms of pulmonary tuberculosis (exclusive of miliary tuberculosis), whether its purpose be for definitive treatment, as an adjunct to operative procedures, for symptomatic relief, or as a therapeutic trial. (Research studies are now being made with the intermittent streptomycin schedules combined with 12 grams of para-aminosalicylic acid (PAS) orally daily, in the hope of still further delaying the emergence of drug resistant organisms)

CONCLUSION

Selecting the type of streptomycin regimen to use in the treatment of pulmonary tuberculosis must be based upon a careful case evaluation including especially an estimation of the type of pulmonary disease present, and its potentialities to respond to therapy.

Above all else, we must consider chemotherapy as only one of the many therapeutic measures available to us, and every effort must be made to define its exact place in the plan of treatment before this drug is prescribed.

RESUMEN

Basándose en la investigación sobre estreptomicina llevada a cabo en el Hospital Fitzsimons se pueden establecer algunas con-

clusiones preliminares sobre el régimen selectivo para los enfermos de tuberculosis pulmonar

1) Debemos usar la serie más corta de tratamiento con estreptomycinina para lograr nuestro propósito a fin de disminuir el número de casos con "resistencia bacteriana"

2) Estas series *cortas* de 30 a 60 días son satisfactorias en la mayoría de los casos con lesiones exudativas recientes

3) Las series *largas* de 60 a 120 días son mejores y a menudo requeridas en los enfermos con tuberculosis caseoneumónica (especialmente en la neumonía tuberculosa lobar aguda o lobular aguda) En estos casos cuando la estreptomycinina puede ser heroica, la "resistencia bacteriana" puede no tomarse en cuenta

4) Estas series *largas* o las *cortas* intermitentes por largo tiempo pueden ser necesarias en la tuberculosis miliar pulmonar con o sin meningitis

5) El plan intermitente usando uno o dos gramos de droga cada tercer día por uno a cuatro meses, dara resultados clínicos y roentegenológicos comparables a los resultados obtenidos con el plan de uno a dos gramos diarios por periodos de tiempo similares sin reacciones importantes a la droga

Ademas el factor importante para retardar la aparición de la *estreptomycinina resistencia* esta demostrado En nuestras series no se encontró caso con resistencia bacteriana dentro de 42 días Solo 3 por ciento se encontró a los 60 dias, 4 por ciento a los 70 dias, 8 por ciento a los 80 días, 18 por ciento a los 90 días, 24 por ciento a los 100 días y 33 por ciento a los 120 días En otras palabras puede usarse este metodo efectivo de utilización de la droga por un periodo prolongado con menos peligro de encontrar "resistencia bacteriana" que en otros regímenes

El régimen intermitente puede usarse por periodos de uno a cuatro meses o mas, ya sea continuamente o en series pequeñas interrumpidas dependiendo del propósito que se tenga De todos los métodos estudiados en el Hospital Fitzsimons parece que el más efectivo para todas las formas de tuberculosis pulmonar (excluyendo las miihres), es éste ya sea que su objeto sea como tratamiento definitivo o como adjunto del quirurgico, como paliativo o como ensayo (Se hacen investigaciones con la combinación de 12 gramos de Acido Para-aminosacilico, (PAS) oralmente a diario, con la esperanza de demorar la aparición de resistencia del germen)

CONCLUSION

La seleccion del régimen de estreptomycinina en tuberculosis pulmonar debe basarse en la cuidadosa valuación del caso especial-

mente del tipo de enfermedad presente y sus potencialidades de respuesta al tratamiento

Sobre todas las cosas debemos considerar la quimioterapia como uno de los muchos recursos disponibles y todo esfuerzo debe hacerse para definir su lugar exacto en el plan antes de que la droga se prescriba

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Factors Influencing the Outcome of Streptomycin Therapy of Pulmonary Tuberculosis*

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Increasingly representative data are becoming available on many phases of the effects of streptomycin therapy in tuberculosis. The American Trudeau Society has recently published the report of its cooperative investigation in pulmonary tuberculosis,^{1,2} and the United States Public Health Service is presently in the process of compiling the results of its streptomycin study. The cooperative investigation of the Veterans Administration, Army and Navy has prepared four reports of its experience for publication,^{3,6} in addition to interim reports and distribution of the *Minutes* of its semi-annual Streptomycin Conferences, of which eight have been held.

The largest of these studies, that of the Veterans Administration, Army and Navy, has permitted a limited analysis of certain variables, such as variations in streptomycin regimen, in a body of clinical data of considerable uniformity. In a summary of its experience from July 1946, to April 1949, totalling 4500 cases of tuberculosis, including 2000 cases of pulmonary tuberculosis, this study has indicated the following:^{6,7}

1 Reducing the daily dosage of streptomycin from 2 grams to 1 gram to 0.5 gram has successively reduced the incidence of all important toxic manifestations, reducing the duration of administration of the drug from 120 days to 60 days to 42 days likewise is associated with reduced toxicity. A reduction of the number of injections into which the total daily dosage is divided has also been associated with decreased incidence of toxicity. These observations apply particularly to vestibular dysfunction, impairment of renal function, dermatitis, and such other manifestations as may be sufficiently severe to compel cessation of streptomycin therapy.

2 Strains of tubercle bacilli resistant to 10 mcgm per ml or more of streptomycin emerge at a fairly regular rate, which appears to be independent of daily dosage in the ranges studied, but definitely related to duration of therapy. At the end of 42 days of daily administration approximately 35 per cent of specimens examined are resistant to 10 mcgm per ml or more, at the end of 60 days, 50 per cent, at the end of 120 days, 75 per cent. Administration of streptomycin alone every third day, or

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combining daily administration with para-aminosalicylic acid (PAS), materially reduces these rates

3 Different tuberculous conditions respond at different rates to streptomycin therapy, and some individualization of therapy appears to be indicated according to the condition to be treated. Whereas data for extra-pulmonary tuberculous conditions are not as complete as for pulmonary tuberculosis, it appears that the relative effect of different streptomycin regimens is much the same for extra-pulmonary tuberculosis as for pulmonary tuberculosis.

4 Considerable uniformity of therapeutic results has been observed in the treatment of approximately 2000 cases of pulmonary tuberculosis on seven different streptomycin regimens, particularly with respect to rates of x-ray improvement, relapse, sputum conversion, and mortality, as well as such clinical signs as reduction of fever, decrease in sputum volume, and weight gain.

5 However, critical statistical analysis reveals certain differences in x-ray response to treatment in essentially homogeneous groups of cases of pulmonary tuberculosis, with slightly but significantly superior results from regimens of higher daily dosage and greater duration.

6 The therapeutic superiority of such regimens, on the other hand, is tempered by the markedly greater toxicity of the larger daily dosages (2 gms./day), and the definitely higher rate of emergence of streptomycin-resistant tubercle bacilli of the regimens of longer duration (120 days).

7 For this reason it is concluded that, whereas the "best" streptomycin regimen has not yet been determined, one gram a day appears to be a satisfactory daily dosage, and that duration of therapy should generally not exceed 42 or 60 days, until procedures designed for delaying the emergence of streptomycin-resistant strains of tubercle bacilli have been adequately standardized.

In the analysis referred to in paragraph five above, of the x-ray changes in cases of pulmonary tuberculosis treated on different streptomycin regimens^{6,7} the important data are as given in Table I.

From these data it is observed that, on the 120-day regimens, there is no significant difference in the incidence of *all* degrees of x-ray improvement, nor any significant difference on regimens of 2 grams a day for 120 and 60 days. Differences in all x-ray improvement are significant for 1 gm. and 0.5 gm. regimens between 120 and 42 day durations, and between the two 42 day regimens. If, in addition to observing the fact of any degree of improvement by x-ray observation, the *degree* of improvement is also taken into account, and the incidence of "*moderate and marked*" improvement is compared among regimens (Part B of Table I), differences of statistical significance are more numerous, and are not present only between the following regimens: 2 grams a day for 120 days and 1 gram a day for 120 days, and 0.5 gram a day for 120 days and 1 gram q. three days for 120 days.

The data collected by the Veterans Administration, Army and Navy have been derived from "summary reports" submitted by

the cooperating study units according to Tables outlined in advance of each semi-annual Streptomycin Conference. Such summary reports have in general permitted little or no cross-tabulation of variables other than those of regimens. For the Seventh Conference, in April 1949, however, some cross-tabulations were possible.⁷ Individual case reports are now being assembled to permit an extension of statistical analysis beyond that hitherto possible in this study.

Table II presents cross-tabulations with respect to x-ray changes, from data gathered for the Seventh Streptomycin Conference for cases of pulmonary tuberculosis treated with streptomycin for 42 days (1 gram a day and 0.5 gram a day for 42 consecutive days, and 1 gram every third day for 120 days). Similar cross-tabulations are not available for regimens which the study employed prior to April 1948, (2, 1, and 0.5 grams daily for 120 days, and 2 grams daily for 60 days).

From Table II it is seen that cavernous cases of pulmonary tuberculosis improve more frequently by x-ray observation, 120 days after the start of therapy, when homolateral collapse is employed than when it is not, with respect to all degrees of x-ray improvement (74 per cent and 61 per cent respectively), and to marked x-ray improvement (22 per cent and 13 per cent respectively). According to the pre-streptomycin course of the disease

TABLE I
COMPARISON OF X-RAY IMPROVEMENT 120 DAYS AFTER START OF
STREPTOMYCIN THERAPY
A All Degrees of X-Ray Improvement

Daily Dose (gms.)	Duration of Treatment (days)	No of Cases	Per Cent Improved		Per Cent Improved	No of Cases	Duration of Treatment (days)
2	120	372	82	—	79	78	60
1	120	398	80	*	70	647	42
0.5	120	121	80	*	60	259	42
1 q 3 d	120	82	76		—	—	—

B Marked and Moderate X-ray Improvement

2	120	372	66	*	52	78	60
1	120	398	64	*	47	647	42
0.5	120	121	57	*	41	259	42
1 q 3 d	120	82	49		—	—	—

In two center columns (per cent improved), chi-square test has been applied to adjacent pairs. * signifies difference is statistically significant, — signifies difference is not statistically significant.

(judged by a comparison of films in the two to three months immediately preceding the start of therapy), regressive disease improves most frequently (80 per cent all improvement, 21 per cent marked improvement), progressive disease almost as frequently (70 per cent all improvement, 20 per cent marked improvement), and stationary disease least (65 per cent all improvement, 13 per cent marked improvement). The difference in response according to predominance of exudation, whether judged to be over or under 50 per cent, is insignificant with respect to all x-ray improvement (68 per cent and 69 per cent), but those cases judged to be predominantly exudative (51 per cent to 100 per cent exudative) have more marked x-ray improvement at 120 days than those judged to be 0 to 50 per cent exudative (21 per cent and 14 per cent, respectively). According to stage of the disease at the start of treatment, moderately advanced cases improve more (82 per cent all x-ray improvement, 30 per cent marked x-ray improvement), and far-advanced cases less (65 per cent all x-ray improvement, 15 per cent marked x-ray improvement). Too few cases of minimal disease (9) are available for comment.

Table III presents similar cross-tabulations for data from the same source (on 42 day treatment cases) with respect to the relationship of certain variables to sputum conversion, both on direct smear and by culture (negative for at least three months in each instance).

There are few surprises in this table. Sputum conversion in all categories is slightly lower percentagewise by culture than by direct smear, conversion is more frequent with collapse than without, although the difference perhaps is not as striking as might have been anticipated, and far-advanced disease has the lowest sputum conversion rates. Comparably analytic data are not available for sputum conversion more than 120 days after the start of treatment.

In Tables II and III questions arise which suggest the relative analytic incompleteness of the data presented. Are cases receiving the benefit of collapse therapy comparable to those not receiving it? What kind of collapse therapy was employed, and when, in relation to the results noted? Is extent of the disease aside from the characteristics listed important? Many other questions will occur to the inquiring physician and scientist, the answers to which would make possible more precise indications for streptomycin therapy, and its employment in conjunction with other standard forms of therapy such as bed rest, collapse therapy, etc. Amberson, in commenting on the data of the Veterans Administration, Army and Navy, has pointed to some areas where more information is needed.⁹

TABLE II
EFFECT OF VARIABLES ON X-RAY CHANGE IN CASES OF PULMONARY
TUBERCULOSIS TREATED WITH STREPTOMYCIN FOR 42 DAYS
(Cross-Tabulations from Table I, Parts C, D, E, F, Minutes of the
Seventh Streptomycin Conference, Denver, April 21-24, 1949)

X-ray Change 120 Days After Start of Treatment															TOTAL CASES	
Marked Impr		Sit -Mod Impr		All Impr		No Change		Worsen Ing								
No	Pct	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct	
A EFFECT OF HOMOLATERAL COLLAPSE																
1 Cavitary Component Absent/Unknown (with and without collapse)																
42	22	98	52	140	74	25	13	24	13	189	19					
83	22	189	52	272	74	32	9	61	17	365	36					
60	13	218	48	278	61	73	16	106	23	457	45					
2 Without homolat collapse																
3 Without homolat collapse																
185	18	505	50	690	68	130	13	191	19	1011	100					
Totals																
B EFFECT OF PRE-STREPTOMYCIN COURSE OF DISEASE																
1 Trend Unknown																
3	11	9	35	12	46	3	12	11	42	26	3					
6	21	17	59	23	80	3	10	3	10	29	3					
2 Disease Regressive																
29	13	109	52	138	65	51	24	23	11	212	21					
3 Disease Stationary																
146	20	366	50	512	70	71	9	153	21	736	73					
4 Disease Progressive																
184	18	501	50	685	68	128	13	190	19	1003	100					
Totals																
C EFFECT OF PREDOMINANCE OF EXUDATION																
1 Extent Unknown																
3	20	5	33	8	53	4	27	3	20	15	2					
51	14	196	54	247	68	66	18	50	14	363	36					
2 0-50% Exudative																
130	21	300	48	430	69	58	9	137	22	625	62					
3 51-100% Exudative																
184	18	501	50	685	68	128	13	190	19	1003	100					
Totals																
D EFFECT OF STAGE OF DISEASE																
1 Stage Unknown																
0	0	1	20	1	20	1	20	3	60	5	*					
2 Minimal																
0	0	5	56	5	56	2	22	2	22	9	1					
3 Moderately Advanced																
67	30	114	52	181	82	19	9	21	9	221	22					
4 Far Advanced																
117	15	381	50	498	65	106	14	164	21	788	77					
Totals																
184	18	501	50	685	68	128	13	190	19	1003	100					

*—less than 0.5 per cent

"It is felt that the figures relating to cavitary component add very little information, largely because they do not afford any data relative to the recency, chronicity, activity, or morphology of the cavity ", again, "It would be desirable to know more about the response (of exudative lesions) in relation to the duration and acuteness of pneumonic lesions ", and again, "The geographic extent of the disease had no apparent effect on the development of drug resistance, and generally speaking it is thought that the character of a lesion is more important than its extent "

To such questions as these, and to many others, numerous independent investigators are applying themselves In the belief that careful analysis of smaller bodies of clinical data than those cited, uniformly observed, may point the way to answers to some of

TABLE III
EFFECT OF VARIABLES ON SPUTUM CONVERSION
IN CASES OF PULMONARY TUBERCULOSIS TREATED WITH
STREPTOMYCIN FOR 42 DAYS
(Cross-Tabulations from Table I Minutes of the Seventh
Streptomycin Conference)

	Sputum Conversion 120 Days After Start SM BY DIRECT SMEAR			BY CULTURE		
	No of Determi nations	Converted No	Pct	No of Determi nations	Converted No	Pct
A EFFECT OF HOMOLATERAL COLLAPSE						
Cavernous Cases Only						
With homolateral collapse	411	133	32	345	87	25
Without homolateral collapse	484	110	23	415	76	18
Sub-Total, cavernous	895	243	27	760	163	21
Cavitary component absent or unknown (with and without homolateral collapse)						
	180	88	49	159	72	46
Totals	1075	331	31	919	235	26
B EFFECT OF COLLAPSE ACCORDING TO STAGE OF DISEASE (Irrespective of Cavities)						
With Collapse						
Minimal	1	1	100	1	1	100
Moderately Advanced	98	51	52	93	38	41
Far Advanced	378	117	31	309	74	24
Sub-Tot with collapse	477	169	35	403	113	28
Without Collapse						
Minimal	7	6	86	5	4	80
Moderately Advanced	121	73	60	111	55	50
Far Advanced	460	80	17	393	62	16
Sub-Tot without collapse	588	159	27	509	121	24
With/Without Collapse						
Minimal	8	7	88	6	5	83
Moderately Advanced	219	124	57	204	93	46
Far Advanced	838	197	24	702	136	19
Totals	1065	328	31	912	234	26

these questions, the experience of the Tuberculosis Service of the Minneapolis Veterans Administration Hospital in the streptomycin treatment of pulmonary tuberculosis has been reviewed, and the balance of this presentation will be concerned chiefly with its results

Methods and Materials

The Minneapolis Streptomycin Study Unit has been a part of the cooperative investigation of the Veterans Administration, Army and Navy since January 1947. Its cases of pulmonary tuberculosis have been selected according to the protocol agreed upon by the cooperating investigators, which provides essentially that cases shall be progressive or at best stationary, and that x-rays shall disclose some exudative component, the more the better. Recent disease is preferred. Minimal disease is usually considered inappropriate for treatment. Activity of the patient is limited to that in effect prior to streptomycin therapy and is maintained at this level during treatment and for four months thereafter. With treatment regimens of different durations, the four-month period immediately following the start of therapy has been arbitrarily adopted as the "treatment period," and follow-up periods of six months each, following this treatment period, have been the standard units of observation in time.

The Minneapolis Study Unit treated its first cases with 2 grams of streptomycin a day for 120 days, beginning in February 1947, and later in that year cases were treated with 2 grams a day for 60 days and then 1 gram a day for 120 days. Observation is possible for 22 months from the start of treatment (the four-month treatment period and three six-month follow-up periods) in 32 such cases, designated as having been treated on "old" regimens. Alternation of treatment on regimens of 1.0 gram and 0.5 gram a day for 42 days was begun in April 1948, and on such "new" regimens observation is available on 25 cases for 10 months (the four-month treatment period and one six-month follow-up period).

These 57 cases, designated as "protocol cases," constitute the principal body of clinical material to be analyzed. Recognizing, however, that the restrictions of the protocol necessarily limit the variety of disease subjected to streptomycin therapy, the Minneapolis Study Unit has analyzed an additional 29 cases, designated as "non-protocol cases" in a manner similar to that applied to the protocol cases.¹⁰ These non-protocol cases are those which had active pulmonary tuberculosis at the time they received streptomycin therapy primarily for extra-pulmonary tuberculosis. In the analysis to follow these 29 cases will generally be considered separately from the protocol cases.

As already intimated, it is believed to be of the utmost importance that classification of cases of pulmonary tuberculosis be as meaningful and complete as possible, particularly with respect to the degree of acuteness of the inflammatory tuberculous process. Designation of stage of the disease, cavitory component, and the pre-streptomycin course do not fully describe tuberculous pulmonary lesions, although "predominance of exudation" is helpful in a rough way.

Desiring to avoid the semantic problem of such terms as exudative, productive, and fibrotic, and agreeing with Medlar¹¹ that "no one phase (of the tuberculous process) is completely independent of its predecessor and all tuberculous lesions do not necessarily undergo the same evolution," the Minneapolis Study Unit adopted a "pathologic" scale of acuteness, consisting of three degrees each of acute, subacute, and chronic inflammatory tuberculous disease, which it has found helpful and meaningful in its

TABLE IV
AGREEMENT AMONG 'JURORS'
As to Classification of Activity of Inflammatory
Process in 26 Cases of Pulmonary Tuberculosis
from '0-Day' X-ray Only
(on 9-point scale)

Points Deviation from Mean	Dr No 1	Dr No 2	Dr No 3	Dr No 4	Dr No 5	Total	Pct Tot
RELATIVELY MIXED							
0	17	11	4	9	10	51	53)
1	4	7	8	8	9	36	37) 90
2		2	1	4	2	9	9
3		1				1	1
Total Ratings	21	21	13	21	21	97	100
Total Deviation	4	14	10	16	13	57	
Avg Deviation	0.19	0.67	0.77	0.76	0.62	0.59	
MIXED							
0	9	3		2	1	15	54)
1	1	2	1	2	4	10	38) 92
2					1	1	8
Total Ratings	10	5	1	4	6	26	100
Total Deviation	1	2	1	2	6	12	
Avg Deviation	0.1	0.4	1.0	0.5	1.0	0.46	
ALL CASES							
0	26	14	4	11	11	66	54)
1	5	9	9	10	13	46	37) 91
2		2	1	4	3	10	8
3		1				1	1
Total Ratings	31	26	14	25	27	123	100
Total Deviation	5	16	11	18	19	69	
Avg Deviation	0.16	0.62	0.79	0.72	0.70	0.56	



FIGURE 1a

FIGURE 1b

FIGURE 1c

Fig 2 (J A) Young World War II White veteran, pulmonary tuberculosis and tuberculous laryngitis—Fig 2a April 2, 1947 disease classed as "unmixed" subacute (almost chronic) (see text)—Fig 2b June 30, 1947 start of treatment with streptomycin (2 gms/day for 120 days), no change in pre-streptomycin period—Fig 2c September 22, 1948 moderate x-ray improvement about 15 months after start of therapy Sputum negative by culture for approximately one year No relapse since

evaluation of the results of streptomycin therapy. A most important part of such a classification is the recognition that nearly all cases fall quite easily into "relatively unmixed" stages of acuteness of the inflammatory tuberculous process, or into "mixed" categories, combining nearly always a definitely chronic component with either an acute or a subacute inflammatory component. In the former as far as can be determined clinically there is relatively little admixture of more than one of the three stages, in the latter a clear mixture of more than one. In this analysis "unmixed" *chronic* cases from the "non-protocol" group have been omitted, and all "unmixed" cases, either protocol or non-protocol have been classified as acute or subacute. A previous report¹⁰ has indicated that "unmixed" subacute "non-protocol" cases appear to respond to streptomycin therapy in a manner almost identical with "unmixed" acute "protocol" cases. Figure 1a illustrates a case of unmixed acute disease, Figure 2a a case of unmixed subacute disease, and Figure 3a a case of mixed disease (combining chronic with acute).

The validity of such a scale of acuteness of the inflammatory tuberculous process has been tested by submitting 26 cases to a "panel" of five physician "jurors," who, without prior experience in such a classification, were asked to rate each case from a single x-ray, without clinical or other data, on a nine-point scale. Table IV summarizes the degree of agreement encountered in this unrehearsed test. It will be seen (bottom line of Table IV) that the average departure from the mean rating of the "jurors" for each case was 0.56 point on the nine-point scale. In only one instance was there a departure from the mean of three points, and in 91 per cent of the ratings there was either perfect agreement with or not more than a one-point departure from the mean. Such a test is not intended to demonstrate accuracy of correlation between x-ray findings and pathology, but does demonstrate, it is believed, that ratings of acuteness of the inflammatory tuberculous process can be made from x-rays by experienced physicians with reliability and validity.

The investigation of the Veterans Administration, Army and Navy has adopted a scale of x-ray change which may be applied to a comparison of any two x-rays of a given patient.

- 1 — marked improvement
- 2 — moderate improvement
- 3 — slight improvement
- 4 — no change
- 5 — slight worsening
- 6 — moderate worsening
- 7 — marked worsening

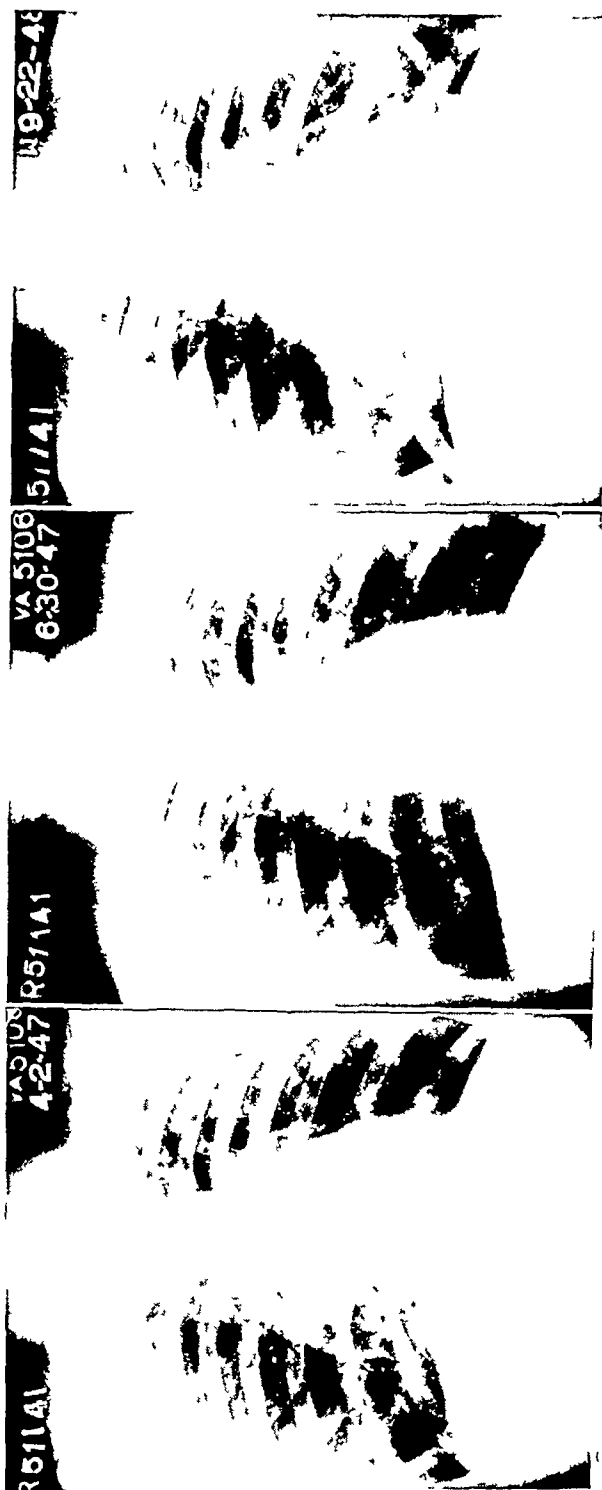


FIGURE 2a

FIGURE 2b

FIGURE 2c

Fig 2 (JA) Young World War II White veteran, pulmonary tuberculosis and tuberculous laryngitis—Fig 2a April 2, 1947 disease classed as "unmixed" subacute (almost chronic) (see text)—Fig 2b June 30, 1947 start of treatment with streptomycin (2 gms/day for 120 days), no change in pre-streptomycin period—Fig 2c September 22 1948 moderate x-ray improvement about 15 months after start of therapy Sputum negative by culture for approximately one year No relapse since

This scale has been employed by the Minneapolis Study Unit, with the slight modification of adding two extremes those of "very marked improvement," and "very marked worsening" (nearly always leading to death) Every effort has been made to make each point on the scale on either side of "no change" uniform in depth or breadth For the purposes of this report the first two points on the Minneapolis scale have been grouped together to constitute "marked improvement"

Figures 1 to 3, in addition to illustrating the major classifications of the scale of acuteness of the inflammatory tuberculous process, also illustrate the degrees of improvement by x-ray observation employed in analysis of data In each Figure three x-rays are shown (a) at the start of treatment, (b) at the end of the 4-month treatment period, and (c) a follow-up x-ray By comparing films (a) and (b) the change in the treatment period may be determined, by comparing films (a) and (c) total change from start of treatment may be rated

The ratings of change in these three cases which have been made by the Minneapolis Study Unit have been as follows

Fig No	Acuteness	Change at 4 months	Follow up Change
1	Acute	Marked improvement	Very marked improvement
2	Subacute	Slight improvement	Moderate improvement
3	"Mixed" (chronic & acute)	Slight improvement	Slight to moderate improvement

Results

Table V gives the results of the analysis of 86 cases of pulmonary tuberculosis according to the characteristics and observations described On the horizontal axis of Part A of this Table are given the defining characteristics of each group, in accordance with the practice of the larger streptomycin study of the Veterans Administration, Army and Navy On the horizontal axis of Part B of this Table are given the results of treatment in each group x-ray improvement (both of all degrees and "marked" improvement), at four months, 10 months, and 22 months after the start of therapy, the incidence of relapse by x-ray observation at the latter two points in time, the extent to which collapse therapy has been employed in the same periods, sputum conversion, either at 10 months or 22 months after the start of therapy, and the cumulative mortality to date

On the vertical axis of Table V, in both Parts A and B, are listed the 16 groups into which the 86 cases have been divided, according to whether each case is

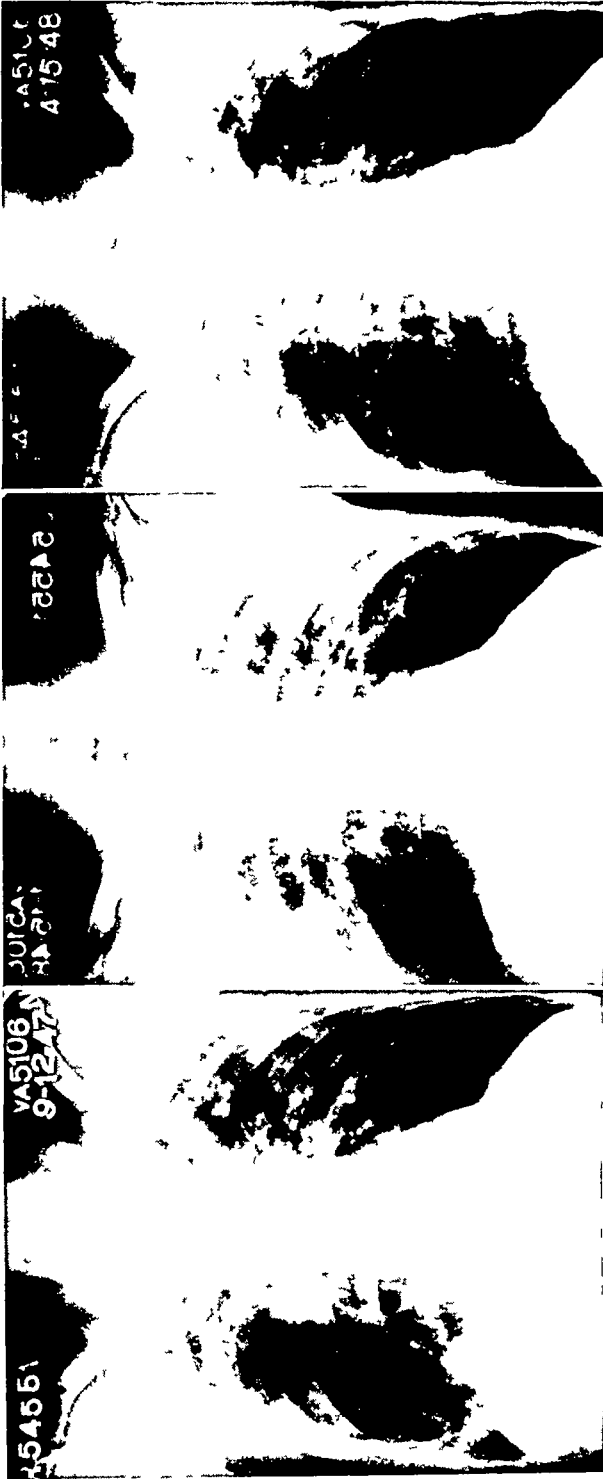


FIGURE 3a

FIGURE 3b

FIGURE 3c

Fig 3 (JP) 55-year-old World War I White veteran, pulmonary tuberculosis, and tuberculosis of tongue—Fig 3a September 12, 1947 approximately stationary disease except for recent spread into right base, classed as "mixed" chronic and acute (see text), just after start of streptomycin therapy—Fig 3b January 15, 1948 very slight improvement at end of streptomycin therapy (2 gms/day for 120 days), and tuberculous ulcer of tongue healed—Fig 3c April 15, 1948 slight to moderate improvement seven months after start of therapy Transferred to another hospital, patient has subsequently had a slight relapse sputum remains positive, but he is still living

"protocol" or "non-protocol"
treated on an "old" or a "new" regimen
treated or not treated with collapse therapy
predominantly "unmixed" or "mixed" with respect to the
acuteness of inflammatory disease

Except for differences in duration of observation after initiation of streptomycin therapy, cases treated on "old" and "new" regimens have been found to be quite comparable, and have been grouped together in lines 17 to 24 of this Table, thus eliminating the variable of regimen. This is in accordance with the finding in the larger study that differences in results according to regimen are relatively slight and less significant than according to other variables, and to the observation of the Minneapolis Study Unit that "It is not felt that any differences between groups are related to dosage and duration of streptomycin therapy"¹⁰

In lines 25 to 28 on the vertical axis of Table V regrouping eliminates the variable of collapse therapy, and lines 29 and 30 give the totals for "protocol" and "non-protocol" cases separately. Line 31 gives the total experience for the entire 86 cases. Groupings from this table other than those indicated are readily available to the interested analyst.

Protocol Cases

From Table V-A it will be seen that there is relatively little difference in defining characteristics tabulated for the 35 "unmixed" cases (Group 25) and 22 "mixed" cases (Group 26), with the following differences being the most important: the "mixed" cases are slightly more far-advanced, and have cavities demonstrable more frequently.

There is a considerable difference between these two groups in clinical results, as is seen in Table V-B. Whereas the "unmixed" cases, with respect to all degrees of x-ray improvement (columns 11, 13, and 16), were 100 per cent improved at four months, 94 per cent at 10 months, and 82 per cent (14 of 17 cases, Groups 1 and 3) at 22 months after the start of treatment, the corresponding figures for the "mixed" group were 73 per cent at four months, 50 per cent at 10 months, and 40 per cent (six of 15 cases, Groups 5 and 7) at 22 months. The figures for the "unmixed" group with respect to marked x-ray improvement (columns 12, 14 and 17) are 26 per cent at four months, 77 per cent at 10 months, and 82 per cent at 22 months. The "mixed" group show marked x-ray improvement in 0 per cent at four months, in 32 per cent at 10 months, and in 33 per cent at 22 months. There is a corresponding disparity for the relapse rates (columns 15 and 18) at both 10 and 22 months after the start of streptomycin therapy for these two

TABLE V A
CHARACTERISTICS DEFINING GROUPS
IMMEDIATELY PRIOR TO START OF STREPTOMYCIN THERAPY

Group No	Treatment Groups	Group Designation*	Number of Cases In Grp	Stage of Disease M A	Mfn	(1)	(2)	F A	Re-gressive	Pre SM Course Sta-tion-ary	(5)	(6)	De-strable	Cavities non-strable	(7)	(8)	Predominance of Exudation 51-100 Pct	(9)	(10)
		(Column No)				(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)				
CASES TREATED ON VA SM PROTOCOL																			
Disease Relatively "Unmixed"***																			
With Collapse Therapy																			
1	"Old" Regimens**, 22 mo F-U	IA1a	11	0	0	11	0	11	1	2	8	8	3	10	1				
2	"New" Regimens**, 10 mo F-U	IB1a	11	0	2	9	1	9	1	1	9	11	0	9	2				
Without Collapse Therapy																			
3	"Old" Regimens, 22 mo F-U	IA1b	6	0	0	6	0	6	0	3	3	2	4	2					
4	"New" Regimens, 10 mo F-U	IB1b	7	0	4	3	0	3	0	1	6	4	3	5	2				
Disease "Mixed"*** (Acute & Chronic)																			
With Collapse Therapy																			
5	"Old" Regimens, 22 mo F-U	IA2a	1	0	0	1	0	1	0	1	0	0	1	1	0				
6	"New" Regimens, 10 mo F-U	IB2a	2	0	1	1	0	1	0	2	0	2	0	2	0				
Without Collapse Therapy																			
7	"Old" Regimens, 22 mo F-U	IA2b	14	0	0	14	1	14	1	3	10	11	3	11	3				
8	"New" Regimens, 10 mo F-U	IB2b	5	0	0	5	0	5	0	0	5	5	0	3	2				
NON-PROTOCOL CASES**																			
Disease Relatively "Unmixed"***																			
With Collapse Therapy																			
9	"Old" Regimens, 22 mo F-U	IIA1a	7	1	1	5	0	5	0	7	0	5	2	1	6				
10	"New" Regimens, 10 mo F-U	IIB1a	1	0	1	0	1	0	1	0	0	1	0	0	1				
Without Collapse Therapy																			
11	"Old" Regimens, 22 mo F-U	IIA1b	8	1	6	1	1	1	1	5	2	1	7	1	7				
12	"New" Regimens, 10 mo F-U	IIB1b	4	0	3	1	0	1	0	4	0	1	3	1	3				
Disease "Mixed"*** (Acute & Chronic)																			
With Collapse Therapy																			
13	"Old" Regimens, 22 mo F-U	IIA2a	2	0	0	2	0	2	0	1	1	2	0	1	1				
14	"New" Regimens, 10 mo F-U	IIB2a	0	0	0	0	0	0	0	0	0	0	0	0	0				
Without Collapse Therapy																			
15	"Old" Regimens, 22 mo F-U	IIA2b	6	0	0	6	0	6	0	3	3	6	0	2	1				
16	"New" Regimens, 10 mo F-U	IIB2b	1	0	0	1	0	1	0	0	1	1	0	1	0				

SUB-TOTALS PROTOCOL CASES													
Disease Relatively Unmixed													
17 With Collapse Therapy	IIa	22	0	2	20	3	17	19	3	19	3	3	1
18 Without Collapse Therapy	IIb	13	0	4	9	0	4	6	7	9	7	9	1
Disease Mixed (Acute & Chronic)													
19 With Collapse Therapy	I2a	3	0	1	2	0	3	0	2	1	3	0	0
20 Without Collapse Therapy	I2b	19	0	0	19	1	3	15	16	3	11	5	5
NON-PROTOCOL CASES													
Disease Relatively 'Unmixed'													
21 With Collapse Therapy	IIIa	8	1	2	5	1	7	0	6	2	1	7	7
22 Without Collapse Therapy	IIIb	12	1	9	2	1	9	2	2	10	2	10	10
Disease 'Mixed' (Acute & Chronic)													
23 With Collapse Therapy	II2a	2	0	0	2	0	1	1	2	0	1	1	1
24 Without Collapse Therapy	II2b	7	0	0	7	0	3	4	7	0	3	4	4
PROTOCOL CASES													
25 Disease 'Unmixed' (lines 17, 18) (Per cent of Group 25)	I1	35 (100)	0 (0)	6 (17)	29 (83)	2 (6)	7 (20)	26 (74)	25 (71)	10 (29)	28 (80)	7 (20)	7
26 Disease 'Mixed' (lines 19, 20) (Per cent of Group 26)	I2	22 (100)	0 (0)	1 (5)	21 (95)	1 (5)	6 (27)	15 (68)	18 (82)	4 (18)	17 (77)	5 (23)	5
NON PROTOCOL CASES													
27 Disease 'Unmixed' (lines 21, 22) (Per cent of Group 27)	III	20 (100)	2 (10)	11 (55)	7 (35)	2 (10)	16 (80)	2 (10)	8 (40)	12 (60)	3 (15)	17 (85)	17
28 Disease 'Mixed' (lines 23, 24) (Per cent of Group 28)	II2	9 (100)	0 (0)	0 (0)	9 (100)	0 (0)	4 (44)	5 (56)	9 (100)	0 (0)	4 (44)	5 (56)	5
TOTALS													
29 ALL PROTOCOL CASES (lines 25, 26) (Per cent of Group 29)	I	57 (100)	0 (0)	7 (12)	50 (88)	3 (5)	13 (23)	41 (72)	43 (75)	14 (25)	45 (79)	12 (21)	12
30 NON PROTOCOL CASES (lines 27, 28) (Per cent of Group 30)	II	29 (100)	2 (7)	11 (38)	16 (55)	2 (7)	20 (69)	7 (24)	17 (59)	12 (41)	7 (21)	22 (76)	22
31 GRAND TOTAL-ALL CASES (Per cent of Total)		86 (100)	2 (2)	18 (21)	66 (77)	5 (6)	33 (38)	48 (56)	60 (70)	26 (30)	52 (60)	34 (40)	34

*--Group designation symbols as follows

I--Protocol Cases A--'Old' Regimens** 1--'Unmixed' Disease** a--with collapse therapy

II--Non Protocol Cases B--'New' Regimens** 2--'Mixed' Disease** b--without collapse therapy

**--see text for definition and explanation

Abbreviations SM = streptomycin F-U = follow up (from start of treatment),

Min -- minimal MA = moderately advanced FA = far advanced

TABLE V B
RESULTS OF STREPTOMYCIN TREATMENT

Group No	TREATMENT GROUPS	Group Designation*	EMPLOYMENT OF COLLAPSE THERAPY AFTER START OF SM TREATMENT**						SPUTUM CONVERSION BY CULTURE (Time After Start SM)			CUMULATIVE MORTALITY FROM PULMONARY TBC (Time After Start SM)					
			0 4 mos		5 10 mos		11 22 mos		At 10 mos		At 22 mos		At 10 mos		At 22 mos		Group No
			No	Pct	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct	No	Pct	
(Column No) (19) (20) (21) (22) (23) (24) (25)																	
CASES TREATED ON VA SM PROTOCOL																	
Disease Relatively "Unmixed"***																	
With Collapse Therapy																	
1	"Old" Regimens**, 22 mo F-U	IA1a	4	36	4	36	3	28	—	—	7	64	0	0	2	18	1
2	"New" Regimens**, 10 mo F-U	IB1a	8	73	3	27	—	—	9	82	—	—	0	0	—	—	2
Without Collapse Therapy																	
3	"Old" Regimens, 22 mo F-U	IA1b	0	0	0	0	0	0	—	—	4	67	1	17	1	17	3
4	"New" Regimens, 10 mo F-U	IB1b	0	0	0	0	—	—	1	14	—	—	0	0	—	—	4
Disease "Mixed"*** (Acute & Chronic)																	
With Collapse Therapy																	
5	"Old" Regimens, 22 mo F-U	IA2a	0	0	0	0	1	100	—	—	0	0	0	0	0	0	5
6	"New" Regimens, 10 mo F-U	IB2a	1	50	1	50	—	—	0	0	—	—	0	0	—	—	6
Without Collapse Therapy																	
7	"Old" Regimens, 22 mo F-U	IA2b	0	0	0	0	0	0	—	—	3	21	5	36	7	50	7
8	"New" Regimens, 10 mo F-U	IB2b	0	0	0	0	—	—	0	0	—	—	3	60	—	—	8
NON-PROTOCOL CASES**																	
Disease Relatively "Unmixed"***																	
With Collapse Therapy																	
9	"Old" Regimens, 22 mo F-U	IIA1a	3	42	2	29	2	29	—	—	7	100	0	0	0	0	9
10	"New" Regimens, 10 mo F-U	IIB1a	1	100	0	0	—	—	1	100	—	—	0	0	—	—	10
Without Collapse Therapy																	
11	"Old" Regimens, 22 mo F-U	IIA1b	0	0	0	0	0	0	—	—	6	75	0	0	0	0	11
12	"New" Regimens, 10 mo F-U	IIB1b	0	0	0	0	—	—	4	100	—	—	0	0	—	—	12
Disease "Mixed"*** (Acute & Chronic)																	
With Collapse Therapy																	
13	"Old" Regimens, 22 mo F-U	IIA2a	2	100	0	0	0	0	—	—	2	100	0	0	0	0	13
14	"New" Regimens, 10 mo F-U	IIB2a	0	0	0	0	—	—	0	0	—	—	0	0	—	—	14

eight "mixed" cases (Groups 13 and 15) followed to this point. The corresponding figures for marked x-ray improvement (columns 12, 14 and 17) are for "unmixed" cases (Group 27), 10 per cent at four months, 50 per cent at 10 months, and 100 per cent at 22 months after the start of therapy, for "mixed" cases (Group 28), 0 per cent at four months, 0 per cent at 10 months, and 12 per cent at 22 months after the start of treatment. Relapse rates at 10 and 22 months after the start of treatment (columns 15 and 18) are correspondingly definitely higher for the "mixed" than for the "unmixed" cases.

Collapse therapy (columns 19 to 21, Table V) has been employed in eight of the 29 non-protocol cases (34 per cent, contrasted with 44 per cent of the protocol cases) in eight of 20 (40 per cent) of "unmixed" cases (Groups 21 and 22), and two of nine (22 per cent) of "mixed" cases (Groups 23 and 24). Types of collapse and time of employment in these 10 cases of collapse therapy were

Period After Start of SM Therapy	UNMIXED CASES			MIXED CASES		
	Thoraco plasty	Pneumo thorax	Phrenic	Lobec- tomy	Thoraco- plasty	Phrenic
0- 4 mos	3	0	1	0	1	1
5-10 mos	1	1	0	0	0	0
11-22 mos	1	0	0	1	0	0
TOTALS	5	1	1	1	1	1

With an even smaller number of cases receiving collapse therapy in the non-protocol group than in the protocol group, it is not possible to draw valid conclusions as to the effect of type of collapse or the time of its employment.

Comparison of the "unmixed" groups treated with and without collapse therapy (Groups 21 and 22, Table V) results in much the same impression of more favorable results for the former (with collapse therapy) as in the case of the protocol cases. Both groups have sputum conversion rates (100 and 83 per cent respectively) higher than corresponding groups (Groups 17 and 18) treated on the pulmonary tuberculosis protocol (73 and 38 per cent respectively). Only one patient of the non-protocol series, in the "mixed" group without collapse therapy (Group 15), has died, between 11 and 22 months after the start of treatment.

Thus it is seen, in the non-protocol cases—admittedly different in many respects from the protocol cases—that the same *relative* differences occur between "mixed" and "unmixed" groups, with and without collapse therapy, as occur in the protocol cases. This

applies generally to all the observations listed in Table V-B x-ray improvement, relapse rates, sputum conversion, and mortality from pulmonary tuberculosis

Discussion

The study of the effects of streptomycin therapy in the treatment of tuberculosis, having passed through the stages of establishing its therapeutic efficacy, avoiding the unnecessarily high incidence of toxicity of the larger dosages, and the unnecessarily high rates of emergence of streptomycin-resistant strains of tubercle bacilli obtained with regimens of too long duration, is now in the more difficult stage of attempting to establish the more precise indications for the use of streptomycin as a part of the overall program of treatment of cases of tuberculosis. It has become increasingly important to determine the types of disease which respond best, as well as the indications for the use of streptomycin in cases where its contribution to a favorable result may be expected to be less striking.

These problems are particularly acute in the treatment of pulmonary tuberculosis. More information is urgently needed especially with respect to the timing of combined streptomycin and collapse therapy. And more data are needed as to the indications for streptomycin therapy according to the type of pulmonary tuberculosis which a patient may have. It is believed that the type of analysis of the experience of the Minneapolis Study Unit here presented may be of assistance in answering these questions.

Methods of classification and evaluation are inseparable parts of the problem. It is believed that the methods of classification ordinarily employed—stage or extent of the disease, estimates of the amount of "exudation," and observations as to the cavitory component—are insufficient for adequate evaluation. Other identifying variables, such as age of the lesion, x-ray observations of confluence, density, and character of a cavity wall, probably all must be taken into account, and in the study of the Veterans Administration, Army and Navy, through the medium of the individual case reports now being collected for analysis, it is hoped that useful information as to the relative importance of these, and more, will be forthcoming.

The experience of the Minneapolis Veterans Administration Hospital has led to the belief that a classification of considerable usefulness concerns an estimate of the acuteness of the inflammatory tuberculous process (from both x-ray and clinical data), particularly as to whether there is present a clear-cut mixture of components which may be designated as chronic, and acute or subacute. In this "mixed" type of case—that with well defined

chronic lesions plus lesions of more recent origin, especially if fibrocavernous disease is present—the outlook, with or without streptomycin, is entirely different from that of the relatively “unmixed” case—that in which the lesions are predominantly acute or subacute, with little or no chronic component. In our experience the recognition of this factor in classification has been more meaningful than almost any other variable.

The problems of evaluation of results are very real, and fully as difficult and as important as those of classification.

“It probably is not an unfair statement to say that no uniform or standard method of reporting results of treatment of any form of tuberculosis has been devised. There is not agreement as to what criteria are the most important, or relatively most important. The usual appraisal is a composite of a number of clinical observations, such as roentgenographic change, sputum examination, clinical signs, and erythrocyte sedimentation rate. In the final analysis *survival without detectable reactivation of the disease under essentially “normal” socio-economic conditions* is the criterion for success of therapy. But obviously there are gradations of efficacy short of this end result which are recognized as satisfactory, and such a criterion, if solely relied upon, cannot be applied until many years have passed.”⁶

In most studies of the effect of streptomycin in the treatment of pulmonary tuberculosis primary reliance has been placed on x-ray improvement and sputum conversions as the best criteria for the success of therapy. Improvement in such clinical signs as disappearance of fever, reduction in sputum volume, an improved general sense of well-being, and weight gain, has been found to be somewhat illusory. No study has yet been followed long enough to establish clearly mortality rates, although it is possible that the application of actuarial life table techniques may even now afford valuable mortality data of differential value.

There can be little quarrel with the validity of sputum conversion as an index of therapy of which streptomycin may be a part. The fact of “x-ray improvement,” however, is more debatably a reliable criterion. Most studies have placed heavy reliance on a comparison of x-rays taken at the start of treatment and at the end of the treatment period, and have tabulated results as improved, unchanged, or worse. Such a method has the great advantage of relative accuracy, but disregards the *degree* of change, which it is believed is fully as important. The cooperative study of the Veterans Administration, Army and Navy, in its latest report,⁸ has emphasized the desirability of taking into account the degree of change, and has attempted to standardize a method of determining this with relative objectivity.

In the 86 cases presented in this report, for example (bottom

line of Table V), it is seen that 90 per cent were observed to have all degree of x-ray improvement (column 11) This figure was almost identical for the cases treated on the pulmonary protocol, primarily for acute and progressive pulmonary tuberculosis (Group 29), and for the cases treated primarily for extra-pulmonary tuberculosis but with active pulmonary tuberculosis present (Group 30), in spite of the fact that the two groups are found to differ markedly in most important characteristics (Table V-A) If all degrees of x-ray improvement are determined also 10 and 22 months after the start of treatment (columns 13 and 16, Table V-B), the difference between Groups 29 (protocol) and 30 (non-protocol) becomes more apparent But it has been our experience that determining the frequency of *marked* x-ray improvement (columns 12, 14 and 17) is a better measure of the effect of streptomycin than the simpler determination of any degree of improvement

In reporting such observations as x-ray change, the incidence of relapse, sputum conversion, and mortality, it is believed that it is important to base these on a single point in time, usually or nearly always the day of starting specific therapy It is believed that such a technique is preferable to recording changes separately for different observation periods, with different basing points (as, for example, "change in follow-up period," which compares between end of treatment and latest follow-up data available, but makes possible no precise comparison with the start of treatment), and will permit simpler and more accurate statistical analysis of results

It is apparent from the analysis presented that streptomycin-treated cases receiving collapse therapy in addition to the antibiotic differ from those not receiving collapse therapy This probably is inevitable, because of the well-established indications and contraindications for collapse therapy, but it does make difficult precise statistical comparison of the groups treated with and without collapse In general, two groups do not receive collapse therapy those less advanced where the indications are absent or slight, and those very advanced where collapse would be desirable but in which it is impossible or questionably possible to induce collapse, for a variety of reasons

Many of the cases in this study classed as "unmixed" acute or subacute cases, even with a cavitory component, responded so well to streptomycin therapy that collapse therapy was not indicated, yet the majority (22 of 35 protocol cases) did receive collapse, usually on the indication that the cavitory component was unlikely to heal without such adjunctive therapy Among the "mixed" protocol cases, those with both chronic and acute

or subacute disease, on the other hand, collapse therapy was induced in only three of 22 cases

The evidence is becoming increasingly clear that in all cases with cavitary components, where streptomycin therapy of itself is unlikely to achieve cavity closure, collapse therapy should be added at a relatively early date if serious relapse is to be avoided and the best opportunity for collapse not lost. In chronic cases our experience has been that the improvement is slight, less than that in acute and subacute cases, but definite, up until approximately eight months after the start of streptomycin treatment, after which relapses become increasingly serious¹⁰. The "mixed" cases as here defined present a combination of these problems: more improvement than "relatively unmixed" chronic cases, because of the effect of the antibiotic on the acute or subacute component present, but early relapse even earlier than in "unmixed" chronic cases, probably related to the fibro-cavernous component which is relatively uninfluenced by the antibiotic therapy.

The kind of case of pulmonary tuberculosis here designated as "mixed" is of course the primary therapeutic problem of almost every institution charged with the care of tuberculous patients. Streptomycin therapy can and does help these patients, but unfortunately only temporarily in a considerable proportion, unless other therapeutic measures, especially collapse therapy, are available and introduced promptly. One may indeed speculate whether if collapse therapy were employed more frequently and more intimately in association with the period of primary benefit from streptomycin, the relapse and mortality rates would not be lower than indicated, and superior overall results achieved, in this group.

The New York State Hospitals group has published a careful analysis of their experience with streptomycin in the treatment of pulmonary tuberculosis, with particular reference to the integration of collapse therapy with streptomycin therapy¹². Their analysis has indicated the broadened indications for collapse therapy with the use of streptomycin, and the desirability of planning the two forms of therapy as a combined program. The New York State Hospitals experience has also been reported according to the variables of acute, subacute, and chronic pulmonary disease, but has not stressed the special problem of the "mixed" case emphasized in this presentation.

Because of the different way in which different pulmonary tuberculous problems respond to streptomycin therapy, the overall results reported for a series will depend considerably on the make-up of the series reported. More recent disease, more acute, less advanced, less cavernous, has results of therapy far superior to those of older, more chronic and far-advanced disease, partic-

ularly of the variety here classified as "mixed" chronic and acute. The size of this particular classification in any series treated probably influences the overall result more than almost any other factor.

Many other variables in the streptomycin therapy of pulmonary tuberculosis have not been mentioned in this report. The race of the patients has not been discussed, although it undoubtedly is a factor. Emergence of streptomycin-resistant strains, use of retreatment with streptomycin, the role of bed rest itself, and probably other important factors, have undoubtedly entered into the results presented. This report has rather attempted to concentrate on certain classification variables, and on a careful method of reporting results, as one approach to the complex problem of evaluation of the results of streptomycin therapy of tuberculosis.

SUMMARY

1) The experience of the cooperative study by the Veterans Administration, Army and Navy of the effects of streptomycin in the treatment of tuberculosis has been briefly reviewed. This investigation has been one primarily of the influence of varying dosage regimens in quite uniform clinical material. It has shown that dosages of 1 gram a day are therapeutically effective, with an incidence of toxic manifestations sufficiently low not to be a serious handicap. It has shown that regimens of 42-day and 60-day duration, while not quite as effective as those of longer duration, are preferable to the latter because of definitely lower incidence of emergence of streptomycin-resistant tubercle bacilli.

2) The method of reporting data in the study of the Veterans Administration, Army and Navy has permitted relatively little evaluation of variables of therapy other than those of regimen. To a limited extent the study has indicated that results are superior when streptomycin and collapse therapy are employed in combination, that disease which is progressive before initiation of streptomycin therapy improves more than stationary disease, and that moderately advanced disease improves more than minimal or far-advanced disease, in comparable periods of time.

3) The experience of the Minneapolis Veterans Administration Hospital with the streptomycin therapy of cases of pulmonary tuberculosis is presented. The material consists of 86 cases of active disease, 57 cases treated according to the Veterans Administration protocol for pulmonary tuberculosis and 29 cases of less extensive disease treated primarily for extra-pulmonary tuberculosis.

4) All cases had a definitely acute or subacute inflammatory tuberculous component, a proportion of these had clear-cut mix-

tures of both chronic disease and more recent disease This "mixed" group of cases was found to have an outcome of therapy definitely inferior to that of the "relatively unmixed" acute and subacute cases, in all categories studied It is believed that it is important to stress this classification in the evaluation of the results of streptomycin therapy in the treatment of tuberculosis

5) In the 86 cases, both those treated and not treated on the pulmonary protocol, results were superior when collapse therapy (thoracoplasty in over half the cases collapsed) was employed in close conjunction with the period of maximum benefit from streptomycin therapy, which in general consisted of the first eight months after the start of antibiotic therapy This was true for both "relatively unmixed" acute and chronic cases and for "mixed" cases, but especially for the latter These observations appear to be largely independent of variations in the five streptomycin regimens employed

6) Evidence is presented to indicate that observation of any degree of x-ray improvement, whether slight, moderate or marked, at the end of the initial treatment period, is a method of evaluation which is inadequate for discrimination of results between regimens employed, or between groups of cases treated It is believed that standardized measures of the degree of x-ray improvement enhance roentgenographic evaluation, particularly in the first months after the start of therapy Sputum conversion rates and relapse rates are important additional criteria for evaluating results In later follow-up periods mortality rates are of increasing value

7) It is concluded that the response of the cavitory component to streptomycin therapy, as to any form of treatment of pulmonary tuberculosis, is the chief factor determining the outcome of a program of therapy in which streptomycin is a part, and that prompt and energetic measures directed toward the control of that component have at present the best opportunity for improving still further the already distinguished achievements of the streptomycin therapy of pulmonary tuberculosis

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Streptomycin in the Treatment of Tuberculosis in Children*

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Streptomycin has been developed into an extremely important place in the treatment of tuberculosis. The medical literature is replete with articles dealing with streptomycin in the treatment of tuberculosis in adults but few articles have appeared concerning the use of this antibiotic in treating tuberculosis in children. Because of the tendency of the past 15 years to pay less attention to the child with primary tuberculosis and to close many of the previously well-occupied children's units in sanatoria throughout the country, it might be expected that streptomycin would find a very insignificant role in this phase of tuberculosis work. However, there are still children with more than the simple primary tuberculosis who require more than an occasional clinic checkup while on a limited exercise routine at home; there are still a fair number of children whose tuberculosis is not confined to hilar nodes, who require sanatorium care and definite therapy. It is these children who provide a place for the use of streptomycin.

At Maybury Sanatorium Children's Unit, streptomycin was made available for emergency cases in April 1947, for research purposes in August 1947, and for all purposes in October 1947. From April 22, 1947 to January 31, 1949, 101 of our 281 children received streptomycin. A review of these children with five months' follow-up in comparison with a similar series comprising 780 children treated in the six-year period from January 1, 1941 to December 31, 1946, forms the basis for this presentation. There is no essential difference in the treatment of the two groups except that streptomycin was used in the 1947-49 group. The same system of classification and the same method of evaluating the results was used in both groups. Streptomycin was not used in the simple primary tuberculosis cases because they have a tendency to recover without treatment and the hazards of streptomycin therapy did not justify its use. The 101 cases treated with streptomycin are divided roughly into the following groups: 1) miliary and meningitis, 2) severe primary, 3) primary with bronchial complication (PBC), 4) reinfection tuberculosis, and 5) extrapulmonary tuberculosis. Streptomycin therapy varied in the different groups and several changes in dosage were made during the period of this study. Of the 101

*From the Wm. H. Maybury Sanatorium, Northville, Michigan

children, 22 had part or all of their streptomycin before transfer to Maybury Sanatorium. We are not presuming to outline the ideal method of using streptomycin but are merely presenting our observation of 101 streptomycin-treated tuberculosis children and describing our present method of administration.

Miliary and Meningeal Tuberculosis

Miliary and meningeal tuberculosis constituted the emergency cases for which the early supply of streptomycin was hopefully allocated. It has been noted that this form of tuberculosis provided a prime indication for streptomycin therapy.^{1,2} Infrequently had there previously been recoveries observed. Of the 50 miliary cases treated during the 1941-46 period only 13 recovered. The recoveries here occurred only in the coarse type but never in the fine miliary cases. Although the fine miliary cases are more likely to develop meningitis it was found to be a common occurrence also in children with coarse miliary lesions.

Miliary tuberculosis is prone to develop in the severe primary and the progressive primary type of case. The sooner streptomycin therapy can be instituted the better are the chances of good results. Even in those children who are potential miliary cases and who show a definite aggravation of toxemia without obvious cause, one should suspect beginning miliary spread and institute streptomycin therapy. Children, even very young children, tolerated streptomycin well—better than adults.

Large doses of streptomycin are indicated in miliary and meningeal tuberculosis. After early schedules were modified by reason of our experience and information received from other workers in the field,^{3,4} a dosage formula based upon body weight was developed. For miliary tuberculosis it is as follows: 55 to 88 mg streptomycin per kilogram (25 to 40 mg streptomycin per pound) per day for three to six months depending upon the occurrence of a definite recession of the disease and then 25 to 44 mg per kilogram (10 to 20 mg per pound) per day for the remainder of the six months period. The severity of the case is used to determine the exact dosage within the formula. The daily amount is divided into two or three doses depending upon the quantity of solution to be injected at each time and the size of the patient. Our standard streptomycin solution is 200 mg to 1 cc of water. 1.5 cc is about the maximum injection which a small child will tolerate.

Six questionable miliary* cases were also treated and four of

*Miliary tuberculosis was classified as questionable when the roentgenogram taken at the clinical onset of the miliary episode showed fairly well defined miliary lesions which were not confirmed by subsequent roentgenograms, streptomycin having been administered in the meantime.

these have no response to the caloric test. These 18 children are alive and doing well. All have completed their course of streptomycin and gastric cultures are negative for acid fast bacilli. Three of the military and four of the questionable military cases have been discharged to their homes. Three children whose military lesions were advanced were left with military fibrotic nodules but without accompanying clinical manifestation of military tuberculosis. Relatively few acute toxic manifestations were experienced in this group but lack of nystagmus to the caloric test developed in nine of the 12 military cases treated and five of these nine also had objective evidence of dizziness.

Meningitis

Four additional cases of military tuberculosis were given streptomycin therapy but there was an associated meningitis and these cases are considered with the nine children who comprise the meningitis group. Two of these developed meningitis while they were under streptomycin therapy for military tuberculosis. One of these had an extremely fine military and normal spinal fluid when intramuscular streptomycin was started. After meningitis developed he was given intrathecal streptomycin in addition to the intramuscular, the total course covered a six months period. The other child was admitted at one year of age with an advanced but coarser military superimposed upon a consolidated upper lobe which was excavating. Spinal fluid was normal at the beginning of streptomycin therapy. Three months later intra-theal streptomycin was added but was not well tolerated. The intramuscular dose was increased from 60 to 96 mg per kilogram per day. She had 151 gm of intramuscular streptomycin in 249 days and 312 mg of intrathecal streptomycin in 156 days. The military lesions became fibrotic, the pneumonic process improved but the spinal fluid findings remained positive for tuberculous meningitis and the cultures continued to be intermittently positive for acid fast bacilli. She was able to stand in her crib and take fluids until a week before she died although irritability, vomiting, and weight loss were progressive. Opisthotonos and increasing elevation of temperature up to 109 degrees F, terminal fever developed and death occurred seven months after the onset of meningitis and ten months after the start of streptomycin therapy. Of the 101 streptomycin treated children this is the only one who died at Maybury Sanatorium.

Besides the four meningitis patients who had associated military tuberculosis, three other children had associated extrapulmonary tuberculosis and two had associated active primary tuberculosis. In only one of these nine children were the symptoms of menin-

gitis severe when streptomycin was started. He was irrational on transfer from a general hospital. One other was admitted to the sanatorium with an advanced miliary and early meningitis. The other seven developed meningitis while in the sanatorium and streptomycin therapy was instituted before the symptoms had reached the stage that one would ordinarily have suspected the disease. The diagnosis of tuberculous meningitis was in all cases confirmed by laboratory tests on the spinal fluid.

After some variation of dosage in the early cases the following formula of streptomycin therapy was established for tuberculous meningitis: i.e., intramuscularly 55 to 88 mg per kilogram of body weight per day for four to six months depending on the clinical and spinal fluid response and then 22 to 44 mg per kilogram per day for the remainder of the six months period. Intrathecal streptomycin 2.5 mg per kilogram per day (up to 50 mg) is given for three weeks, then the same dose three times per week for three months, and then one-half that dose twice a week for two months. If intrathecal streptomycin could not be given the intramuscular dose was increased to 100 mg per kilogram per day. The intrathecal injections were given after the spinal pressure had been reduced to normal by withdrawal of fluid, the proper amount of streptomycin was injected in 5 cc of water.

Five children, now 26 to 19½ months after the onset of meningitis, have recovered and gone home. One, as mentioned above, is deceased. The three who remain in the sanatorium are free from symptoms and spinal fluid findings of meningitis. All have completed the streptomycin course. One child who had associated tuberculosis of the dorsal spine received no intrathecal streptomycin and two others had less than 10 intrathecal doses. All nine children have loss of equilibrium by the caloric test but have compensated well. One child, the first case, became deaf.

There is still some controversy over the use of intrathecal streptomycin in treating cases of tuberculous meningitis, one argument against its use being that streptomycin is a very irritating substance and, therefore, likely to produce neural damage. However, it is known that meningitis develops in children receiving streptomycin by intramuscular injection—two such cases are included in this series—therefore, it would seem that something more than intramuscular streptomycin was needed in treating the condition. Levinson reports 11 deaths in 19 children treated by intramuscular streptomycin alone.⁵

In the series of cases treated prior to streptomycin 39 had meningitis and all 39 died within a month after the condition was diagnosed. There is no possibility of comparing the condition of these recovered meningitis children with those not treated with

streptomycin and, therefore, it may be that at least some of the neural damages are due to the meningitis and not altogether to the drug. In our experience there is also no evidence to support the claim that intrathecal streptomycin produces either a greater incidence or a more profound type of vestibular damage than large intramuscular doses alone.

Severe Primary Tuberculosis

Severe primary tuberculosis with extensive parenchymal involvement in small children provides a definite indication for streptomycin therapy. The simple primary cases have a tendency to recover spontaneously. They can well be handled in the home. Streptomycin is not indicated in these children but they must be followed carefully for signs and symptoms of exacerbations of the *primary or complications such as milary, bone and joint, or other tuberculosis*. The child who has primary tuberculosis and symptoms of pneumonia may have either a superimposed non-tuberculous infection or an acute increase in his tuberculosis. If a trial of penicillin and other measures does not result in prompt clinical and x-ray improvement one should not hesitate to start streptomycin. The formula for therapy in these cases is as follows: 33 to 66 mg per kilogram of body weight per day for four to seven days or until there has been a satisfactory effect, then one-half that dosage three days a week for the balance of 42 doses. The determination of the number of daily doses and the size of the individual injection is made again on the basis of the size of the child and the maximum dose of a 200 mg per cc solution which he would tolerate. The response to streptomycin will in most cases be quite prompt so that after four to seven days the initial concentrated therapy may be reduced. Even though the clinical progress may be excellent, one must not forget the possibility of these cases developing milary or meningeal tuberculosis and must keep constantly on the watch for signs of these complications.

Five children having severe primary tuberculosis and ranging in age from two to six months were treated with streptomycin. Some received as high as 250 mg per kilogram per day. Only one of the five has a completely normal response to the caloric test but all have normal hearing. Three have gone home and they seemed well compensated at the time. One of the two children still in the sanatorium is well compensated but the other who was the one receiving 250 mg per kilogram is now 14 months of age, will undoubtedly have some difficulty when he starts to walk. With our present dosage we might well have prevented this vestibular damage and still have had the tuberculosis run a favorable course.

Primary with Bronchial Complications (PBC)

Nearly 20 per cent of children admitted to Maybury Sanatorium present the dense, homogeneous, lobular, or lobar shadow of the so-called epituberculosis. This x-ray appearance is due to the combination of a large, active, primary, parenchymal focus, tuberculous, peri-bronchial lymph nodes, and some bronchial interference to pulmonary aeration and drainage. Post-mortem examinations of some of these children, dying of miliary and meningeal tuberculosis, demonstrated the bronchial factor as did bronchoscopic examination in many cases.⁶

In 1941 an analysis was made at Maybury Sanatorium of 42 of these children⁶ who were examined bronchoscopically. Thirty-one, or 74 per cent, were found to have involvement of the bronchi in one or more of the following forms: extrinsic pressure from enlarged lymph nodes, tuberculoma, ulceration, edema, and redness. Decreased ciliary action in the abnormal bronchus and weak expulsive power in the poorly aerated lung distally may allow the secretions to become inspissated and to act as a plug. In five cases a caseous lymph node draining through a bronchial sinus was observed. Sputum (gastric cultures) of 30 children contained tubercle bacilli and usually this persisted over many months. Forty-one had a positive tuberculin test (one not tested). All showed enlargement of the hilar lymph nodes by x-ray. Thirty-five per cent had the left lung and 65 per cent the right lung involved, the left upper and the right upper and middle lobe were most often involved. The involved lobe was of normal size in 45 per cent, smaller than normal in 50 per cent, and larger than normal in five per cent of the cases. Other than wheezing, most children presented almost no protracted symptoms during the long course of x-ray clearing unless marked progression of the parenchymal lesion, and/or extension by bronchial, lymphatic, or hematogenous routes occurred. Twenty-eight per cent of these 42 children were dead at the end of a ten-year period.

Even children in this group who had a relatively uneventful course were found to have more residual damage than had been suspected by the eventual clearing of the x-ray. In 1945, a bronchographic study was made of 34 children having the above mentioned x-ray, clinical, and bronchoscopic history. Bronchiectasis was demonstrated in 24, or 70 per cent of them. It was confined to the lobule, or lobe, which was the site of the previously observed primary disease, and extended from the hilum to the periphery. Twenty-two of these children with only lobular involvement had presented no obvious symptoms of bronchiectasis while one with involvement of the entire middle lobe and the antero-

lateral segment of the right upper lobe had experienced only occasional bouts of fever and cough but had rales over the affected area most of the time. The other child with involvement of the entire right lung had repeated severe attacks of pneumonitis.

Because of the tendency of these lesions to spread, the high percentage of deaths, and the incidence of bronchiectasis in the affected areas it was desirable to investigate the use of streptomycin in the early treatment of this type of case. In August 1947, the American Trudeau Society provided streptomycin for this purpose. Nineteen children were placed in this research group. All had the typical x-ray findings of large hilar lymph nodes and lobar, or lobular, consolidation, 14 had positive sputum cultures at the beginning of streptomycin. In 17 bronchoscopic examination was done, 11 were found to have narrowing of the bronchial lumen and six only excessive secretions. The mean dosage formula used in these cases was as follows: 30 mg streptomycin per kilogram body weight per day given in three equal injections daily for a period of three months. Table I shows the comparison of these 19 Trudeau-Streptomycin-treated children with 26 similar cases admitted to Maybury Sanatorium during the year 1941.

The results seemed good enough that 16 subsequent children

TABLE 1
EVALUATION OF STREPTOMYCIN IN PRIMARY TUBERCULOSIS
WITH BRONCHIAL COMPLICATION

A Control Series 101 children admitted to Maybury 1941 (12 mo) plus 6 year follow-up			
B Streptomycin Series 164 children in Maybury 8-1-47 to 2-13-48 (6½ mo) plus 13½ mo follow-up Average and mean dose, 30 mg/kilo/day for three months			
	A CONTROL		B STREPT
No with typical x-ray	26		19
No bronchoscoped	15		17
1 Redness and secretions only	3 (20%)		6 (35%)
2 Encroachment on lumen visible	12 (75%)		11 (65%)
<i>Parenchymal clearing of more than 50%</i>			
1 in three months	7	(29%)	8 (42%)
2 in six months	11	(48%)	12 (63%)
3 in 20 months from beginning of series	16	(62%)	17 (90%)
<i>Status 20 months from beginning of series</i>			
1 dead	4	(15%)	0 (0%)
2 at home, doing well	6	(23%)	13 (68%)
3 in sanatorium, condition good	15	(58%)	6 (32%)
4 in sanatorium, progress poor	1	(4%)	0 (0%)
Number Bronchograms	7		2
Bronchiectasis	5 (71%)		1 (50%)

with this type of lesion were given streptomycin after the research project was completed in February 1948. The dosage formula in these 16 is more nearly that in use at the present time, namely 15 to 33 mg per kilogram (7 to 15 mg per pound) body weight per day daily for four to seven days, then 15 to 22 mg per kilogram (7 to 10 mg per pound) per day three times a week for a total of 42 days over a period of about three months.

All of these 35 children are alive. 27 of them have gone home and the remaining eight are asymptomatic and making satisfactory progress. None has become deaf and only one has vestibular damage. This child was five months old, had an associated questionable military tuberculosis and received 41 mg per kilogram per day for 61 days. Two children had occasional circumoral paresthesia and two transient joint stiffness.

Our impression of these 35 streptomycin treated children in comparison with the 26 admitted in 1941 may be summed up as follows: 1) the rate of clearing of the parenchymal lesions was bettered by 15 per cent in three months and by 30 per cent in 20 months, 2) the rate of recession of the tracheobronchial lymph nodes was not influenced appreciably, 3) spread to other parts of the lung or body was eliminated, 4) the mortality rate was reduced to zero during this 23 months period, 5) the incidence of bronchiectasis may be reduced but a longer follow-up will be necessary to demonstrate the incidence, 6) streptomycin in our present dosage formula is not likely to cause vestibular damage or to preclude a therapeutic response to a second course should it be needed later, 7) sputum conversion occurred more promptly with streptomycin, 8) endobronchial lesions cleared much more rapidly with streptomycin but the effect on narrowing due to pressure of enlarged tracheobronchial lymph nodes was not remarkable.

Reinfection Type Tuberculosis

Four to eight per cent of the children admitted to Maybury Sanatorium have pulmonary lesions which are classified as reinfection type tuberculosis, i.e., there are no active tuberculous nodes at the hilum and deposits of calcium are often found. In other instances the child had a known positive tuberculin reaction with a simple primary lesion shown by x-ray a year or so previously. These differ from the extended and complicated primary lesions in which the pulmonary infiltrations are associated with definite hilar adenopathy and are a part of the original process. A differentiation is essential because the method of treatment usually applied in reinfection cases is contraindicated in all primary cases. The x-ray findings in the child with reinfection tuberculosis are almost identical with those in the adult with cavitation.

quite a prominent feature. The symptom picture is also similar. They tend to progress badly without active therapy. Streptomycin in these cases must be used in conjunction with collapse therapy or surgery as part of a carefully planned course of treatment. One must be certain that the streptomycin effect is being sought at the proper time with reference to the success of the collapse because resistant strains of tubercle bacilli emerge in these cases as readily as they do in adults, after which further streptomycin therapy is useless. In the event the patient is a six-year old child with a large cavity one must evaluate the chances of closing that cavity successfully with phrenic paralysis, pneumothorax, pneumoperitoneum, or resection of the diseased lobe or lung, or of temporizing with one or more of those collapse procedures until the patient reaches the age at which permanent collapse by thoracoplasty might be considered, i.e., 16 to 18 years depending on the completeness of bone maturity demonstrated by x-ray.

A few of the lesions encountered in children are such that phrenic paralysis or pneumoperitoneum will suffice but in the advanced cases more extensive collapse or surgery must be used. Pneumothorax has a fairly good possibility of controlling lesions of moderate extent with small cavities, but when the lesions are extensive or the cavities large there is a definite limitation on the effectiveness of this type of collapse. Another limitation is the improbability of pneumothorax providing successful control of the lesion through the critical adolescent period up to thoracoplasty age. In a six-year old child we try first to control the lesion without pneumothorax since even a five-year course of pneumothorax at this time would have burned this bridge when it might be more desperately needed between 11 and 16 years.

Because prolonged treatment must be anticipated in many of these cases the possibility of needing more than the usual course of streptomycin treatment must always be considered. In preparation for a resection the streptomycin should be given intensively for a week before the operation and six to 10 days afterward, i.e., 22 to 66 mg per kilogram per day in one to three divided doses. In other cases the streptomycin formula is 15 to 33 mg per kilogram body weight per day, daily for four to seven days and then 15 to 22 mg per kilogram per day three times a week to a total of 42 doses over a three months period.

Five children, five to 11 years of age, among the 101 streptomycin treated children had collapse measures or pulmonary resection. Two had left pneumonectomy, they became asymptomatic, negative on gastric culture, and have gone home. Both had been in the sanatorium for some time before streptomycin became available and had a shrunken lung, extensive bronchiectasis, and

consistently positive sputum They received the drug only at the time of operation 27 and 33 mg per kilogram per day for less than two weeks The other three children were treated with collapse measures and two courses of streptomycin One who had soft non-cavitative bilateral lesions cleared satisfactorily and became negative on gastric cultures with the first course Had collapse therapy been used at that time relapse probably would not have occurred However, the disease did reactivate and now with his second course of streptomycin he is receiving pneumoperitoneum and para-aminosalicylic acid (PAS)

A five year old girl was admitted with two large cavities near the chest wall on the left With streptomycin the cavities became smaller and left phrenic paralysis was performed during the first course Serial x-rays have continued to show steady improvement Five and one-half months after admission she was given another course of streptomycin and pneumoperitoneum was added She has had a recrassh of the left phrenic nerve For almost a year the cavities have not been seen by x-ray and except for one time the gastric cultures have been negative for tubercle bacilli Bed rest (modified by the child) is still in effect Equilibrium and hearing are normal The fifth case was a small, seven-year old child who had soft exudative lesions throughout both lungs and a 5 cm cavity with a fluid level in the right antero-lateral segment With streptomycin the cavity immediately became smaller and right phrenic paralysis and then pneumoperitoneum were added with the result that three months after admission the cavity was invisible by x-ray but gastric cultures did not convert Three months later coincident with the earliest return of right phrenic nerve function and while the hemi-diaphragm was still markedly elevated the cavity reopened The second course of streptomycin was started and right pneumothorax attempted This was abandoned because of adhesions and she was then transferred to the surgical unit for resection

Nine consecutive reinfection cases were treated in the 1941 series before streptomycin was available with four deaths and five recoveries

The final results of streptomycin therapy are not yet known but it is expected that at least part of the good early results may be continued so that a greater proportion of these unfortunate children may recover

Extrapulmonary Tuberculosis

In the extrapulmonary group there are included 13 bone and joint, two lymph adenitis with sinus, one kidney two pleuritis one pericarditis, and two peritonitis cases

The bone and joint cases were given the usual immobilization treatment with surgery as indicated. Streptomycin therapy was not so intensive as in some of the other groups but was continued for longer periods because the bone response is slow. The early cases were treated with the following dosage formula: 15 to 33 mg per kilogram body weight per day for 42 days, given in one or more daily injections. At present the formula is 15 to 33 mg per kilogram per day daily for four to seven days then three times a week to a total of 42 doses over a period of three months in the mild cases with no bone destruction and in cases which show prompt disappearance of signs and symptoms. In destructive bone lesions it is given three times a week for 84 doses over a period of about six months. All accessible accumulations of pus are evacuated and when possible, as in the case of a tuberculous rib, the diseased tissue is excised. In cases of empyema 22 mg per kilogram of body weight is instilled intrapleurally after each aspiration, under intramuscular streptomycin therapy. Decortication may be carried out. At the time of operation for any extrapulmonary condition 33 mg of streptomycin per kilogram of body weight is left in the site of operation.

All of these children are alive and all show definite improvement in the lesions. Eight of the 21 children have gone home and the ones in the sanatorium are in good condition. Five had surgery as follows: one fusion of the spine and removal of a portion of tuberculous rib, one fusion of the hip, one decortication for empyema, one nephrectomy, and one pericardial resection. Other bone and joint cases are continuing on immobilization until they are old enough for fusion. Four children had two courses of streptomycin with good results each time.

Because this is a small series it has not been possible to compare streptomycin treated cases with parallel cases treated without it but several observations have been made: 1) general and local improvement is more prompt, 2) there is a decreased tendency to abscess formation and abscesses already present seem to disappear more readily, 3) the bone changes reach the regenerative stage earlier, 4) streptomycin must not be considered as a substitute for any recognized form of therapy but merely as an adjunct to it, 5) the long term results are not yet known.

Discussion

Streptomycin has a rather wide range of use in treating tuberculosis in children. It is mandatory in the treatment of meningitis and miliary tuberculosis. Its next most important use is in the early treatment of tuberculous spreads. Diligence in the detection of new lesions at the earliest possible time cannot be overemph-

asized It is indicated in acute pulmonary lesions except in simple primary cases and is used effectively in most extrapulmonary tuberculosis It has a place in the pre- and post-surgical programs The effect from its use at Maybury Sanatorium has generally been good as shown in Table 2

The death rate at Maybury Sanatorium has been reduced from 98 per cent for a six-year period and 15 per cent for a 26-month period without streptomycin to one per cent for the first 26-month period during which we have had streptomycin The deaths in meningeal tuberculosis were reduced from 100 per cent to 11 per cent in this same period This reduction in mortality is no doubt due to the fact that treatment was started early and would have been less dramatic had it been used in the more progressed type of case Deaths in miliary tuberculosis were reduced from 74 per cent for a six-year period and 88 per cent for a 26-month period without streptomycin to 6 per cent for the 26-month period with

TABLE 2
MORTALITY IN SANATORIUM CHILDREN
Prior to Streptomycin
Six Years 1-1-41 to 12-31-46
Follow-up to 3-1-47

	Number	Death	Per cent
All Cases	780	77	98
Miliary	26	13	50
Miliary-meningitis	24	24	100
Meningitis	15	15	100

24 Months Comparison Period, 3-44 to 3-46
Follow-up (2 months) to 3-31-49

All Cases	200	30	15
Miliary	10	8	80
Miliary-meningitis	7	7	100
Meningitis	3	3	100

During Streptomycin

21 Months 4-22-47 to 1-31-49
Follow-up (3½ months) to 6-16-49

All Cases	281	2	07
101 Streptomycin Treated Cases			
Miliary	12	0	0
Miliary-meningitis	4	1	25
Meningitis	5	0	0
Other Cases	80	0	0

streptomycin The fact that only one death has yet occurred among the streptomycin treated children is interpreted as meaning that life has been preserved but not necessarily that death has been prevented, it may occur later as the result of tuberculosis Streptomycin does not prevent the development of new tuberculous lesions or spreads nor does it give complete assurance against the reactivation of already treated lesions Evidence has recently been presented to show that the addition of promizole to streptomycin therapy will prevent the development of meningitis in miliary tuberculosis cases, will reduce the incidence of neurological sequelae and will reduce the proportion of relapses⁸ Streptomycin becomes less potent in proportion to the age of the lesions and is almost ineffective against caseous lesions It cannot compensate for the lack of other good treatment but merely supplements it The adequate drainage of all abscess pockets is necessary to a good streptomycin effect Streptomycin is a toxic substance and must be used cautiously

Children tend to tolerate large doses of streptomycin relatively better than adults but they do demonstrate acute toxic and neurotoxic manifestations When streptomycin is to be used as a life saving treatment it must be given in whatever dosage is necessary despite the risks of loss of equilibrium In other cases the dosage should be held below 35 mg per kilogram body weight per day Children do learn to compensate for the loss of equilibrium but it is not reasonable to subject them to this disability if safe dosage will provide a suitable therapeutic result

TABLE 3
TOXIC REACTIONS AMONG 101 CHILDREN
RECEIVING STREPTOMYCIN

	No	Hearing Lost	Caloric Test Positive
Meningitis	9	1	9
Predominantly pulmonary (exclusive of PBC)	36		
1 Miliary	12	0	9
2 ? miliary	6	0	4
3 Babies 2-6 months	5	0	4
4 Others	13	0	0
Primary with bronchial complication (PBC)	35		
1 Trudeau series	19	0	1
2 Others	16	0	0
Predominantly extrapulmonary (exclusive of meningitis)	21	0	0

Intensive therapy for longer than 28 days carries the possibility of streptomycin resistant tubercle bacilli emerging and curtailing further therapeutic value of the drug. For this reason initial periods of intensive treatment must be well limited except in those cases in which the clinical effect is delayed and prolonged high dosage is indicated.

The dosage formula given for each group of cases reported is the result of modifying the various early dosage schedules and arriving at one which experience had shown to be suitable. These formulae may be changed in the future based upon further observations but at the present they are the ones being used at Maybury Sanatorium. They are therapeutically sound and are recommended for use by others in treating cases similar to those reported above. Dihydro-streptomycin is reportedly⁹ less toxic than the earlier preparations used in this study and may permit the use of more intensive therapy without the hazards of toxic manifestations. The emergence of resistant organisms is apparently as likely with dihydro-streptomycin as with the regular variety. Combined treatment with other chemotherapeutic agents may also modify the dosage schedules and the results. The results of streptomycin therapy have ranged from dramatic recoveries from tuberculous meningitis to disappointing failures in caseating glands but generally they were good. Many children are alive and well because they were treated with streptomycin, many others are recovering. It is anticipated that further good results will be recorded in the future.

Comment

From April 1947 through January 1949, 101 children at Maybury Sanatorium were treated with streptomycin and the results compared with a similar series treated previously in an identical manner without streptomycin. The 101 children included military and meningeal cases, severe primary, primary with bronchial complications, reinfection and extrapulmonary cases. The military and meningitis cases were given intensive streptomycin therapy at the earliest possible time after the onset of symptoms. The formula for intramuscular therapy was 55 to 88 mg per kilogram of body weight per day for three to six months depending upon the effect and then 25 to 44 mg per kilogram per day for the balance of six months. The daily amount was divided into two or three doses according to the size of the child. The meningitis cases were also given intrathecal streptomycin according to the following formula: 25 mg per kilogram, up to 50 mg maximum, daily for three weeks then the same dose three times per week for three months and then one-half that dose twice weekly for the balance of six months.

The same courses were repeated in case of relapse. Eighteen cases of military tuberculosis, nine of meningitis, and four of military-meningitis were so treated. All military and meningitis cases and three of the military-meningitis cases survived and were apparently recovered at the end of the survey, May 1, 1949. One military-meningitis case expired in relapse after making satisfactory early improvement. All had vestibular damage, all compensated well, one is deaf. In the previously treated comparison series, 100 per cent meningitis and 80 per cent military cases had died.

Streptomycin was given to five babies with severe primary tuberculosis using the formula of 33 to 66 mg per kilogram body weight for four to seven days and then one-half that dose three times per week for the balance of 42 doses with satisfactory results. Three recovered completely and two were still making good progress in the sanatorium at the end of the study period.

Nearly 20 per cent of the children admitted to the sanatorium were of the primary with bronchial complication type (extensive epituberculosis). In the previously treated comparison series, 15 per cent had died in the two-year and 28 per cent in a ten-year follow-up study. Bronchial obstruction of various types was found in 74 per cent of the cases. Seventy per cent of them were later found to have bronchiectasis in the involved area. Thirty-five children with this type of tuberculosis were given streptomycin using the following formula: 15 to 33 mg per kilogram daily for four to seven days, then 15 to 22 mg per kilogram three times a week for a total of 42 doses over a period of about three months. All 35 children survived and apparently recovered. None suffered any demonstrable vestibular damage. In comparison with the series treated in 1941, the results were as follows: the rate of resolution in the parenchymal lesions were bettered by 15 per cent in three months and by 30 per cent in 20 months, the rate of recession in the tracheo-bronchial nodes was not appreciably changed, spreads to other parts of body, prevalent in the comparison series, was eliminated completely, the mortality was reduced to zero over a 23-month study period and it is anticipated that future studies will show a marked reduction in the incidence of bronchiectasis. Sputum conversions occurred more promptly and endobronchial lesions cleared much more rapidly.

About six per cent of the children admitted by Maybury Sanatorium have reinfection type pulmonary tuberculosis. Five such cases, ranging in age from five to eleven years were included in the 101 cases treated with streptomycin. Besides streptomycin using the same formula as above these children were given collapse or surgical therapy. All five children have survived and all but one give promise of recovery. In the 1941 series four out of

nine children expired within two years. In the extrapulmonary group were included 13 bone and joint, two adenitis with sinus, two pleuritis, two peritonitis, one pericarditis, and one renal tuberculosis cases. In addition to streptomycin each child received all other indicated therapy. The streptomycin dosage formula was 15 to 33 mg kilogram daily for four to seven days and then three days per week for a total of 42 or 84 dose-days depending upon the response. In the empyema cases, 22 mg per kilogram were instilled into the pleural space following aspirations. All 21 children survived and made better than previously observed progress.

The overall results of streptomycin therapy in 101 children, observed over a period of 23 months was good. The death rate was reduced from 15 per cent for a comparable 26 month period to 1 per cent. Only one death occurred in the 101 cases treated. A good chance of recovery is given every child with tuberculosis, even miliary and meningitis cases if adequate treatment can be started early and continued for six months or more.

SUMMARY

The results of treating 101 cases of tuberculosis in children with streptomycin in comparison with previously treated cases is reported. The treatment programs used in five different types of cases are outlined including the recommended streptomycin dosage formulae. The results of therapy in each group of cases is recorded with comparative death rates. The unfavorable effects of streptomycin and the precautionary methods are discussed as well as therapeutic limitations.

RESUMEN

Se refieren los resultados del tratamiento de 101 niños con tuberculosis por medio de la estreptomicina, en comparación con casos tratados anteriormente. Los planes de tratamiento usados en cinco tipos de casos diferentes se describen, incluyendo las dosificaciones de estreptomicina recomendadas.

Los resultados del tratamiento en cada grupo son presentados con los coeficientes de mortalidad comparativamente.

También se presentan los resultados desfavorables y se discuten las precauciones así como las limitaciones terapéuticas.

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Streptomycin Dosage in the Treatment of Tuberculosis

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The efficacy of streptomycin in the treatment of many forms of clinical tuberculosis has been established. The early successes with this measure were achieved with the use of two grams or more, given daily in divided doses, over a period of many months. With this regimen, loss of vestibular function, complete and permanent, was to be expected. Renal irritation with a few cases of serious and even fatal renal damage, a high incidence of allergic manifestations, chiefly dermatologic, pain and induration at the site of injection, facial paresthesias and other toxic effects were also observed. In view of the severity of the disease for which streptomycin was being administered in most cases and the importance of getting the maximum therapeutic response from any agent given in conditions with such poor prognosis, the toxic consequences of large doses of streptomycin were accepted as necessary concomitants of the treatment. These ill effects, together with high cost and restricted supply of streptomycin limited the use of this agent to those patients with the most urgent indications and adequate financial resources.

Streptomycin usually causes a decrease of fever and of tachycardia, cough, sputum volume and bacillary content. These effects are most marked in the early weeks or months of treatment. Complete healing, with disappearance of all abnormal densities on x-ray, cavity closure, sputum conversion and arrest of tuberculosis as a result of streptomycin treatment alone has been, unfortunately, an uncommon experience. More often the streptomycin has merely diminished the acute inflammatory exudate in the lungs and prepared, or assisted, the patient to profit from further collapse measures, or has resulted in subsidence of complications such as laryngeal or tracheobronchial ulceration, intestinal tuberculosis, draining sinuses, etc.

If pulmonary lesions remain active such complications are apt to recur or develop anew at a later date. Recurrences do not appear to be prevented by prolongation of the original course of treatment. Accordingly, it has been recommended that streptomycin be given in courses of six weeks or less at a time instead of the

*From the Western Trudeau Streptomycin Laboratory, Olive View, California, aided by Research Grants 541 and 1104 United States Public Health Service

original recommendations of three or more months continuously. Such short courses may give results little inferior to those of the longer courses and leave the patient with organisms still susceptible to streptomycin.

Animal experiments showed that large doses and frequent administration to maintain continuously high blood levels of streptomycin were not necessary for optimal therapeutic effects. Extensive clinical experiences demonstrated that 1.0 gram doses given in one or two injections daily, yielded clinical therapeutic effects indistinguishable from those obtained with the larger doses and more frequent administrations, with marked decrease in the incidence and severity of toxic manifestations. Further reduction in dosage to 0.5 gram in one injection daily revealed similar effectiveness, with absence of vestibular and visceral toxicity. With the lowering in cost, and increase in availability of streptomycin, this elimination of most of its ill effects greatly extended the indications for its use in the treatment of tuberculous lesions.

Clinical and laboratory investigations at the Olive View Sanatorium have demonstrated the lower limits of therapeutically effective dosage. Amounts of 0.1 gram or less, given daily, were found to be insufficient, producing little of the symptomatic or objective improvement generally observed with larger doses of streptomycin. Administration of 0.2 gram per day gave evidence of therapeutic effect in the majority of patients so treated but failed in a small number who later responded to still larger doses.

If streptomycin is to be given daily, doses of 0.33 gram are well tolerated, and adequate, above the minimal effective dose, with practically no toxicity. If it is given at greater intervals it becomes important to know how large a dose may be given at a single time and what is the least amount which might be effective, and to determine what intervals may be designated.

Although as much as 10.0 grams of streptomycin have been given over a 24 hour period, this might be fatal if administered in a single dose. Single intramuscular injection of 3.0 grams at one time have been given repeatedly without serious consequences. However, doses of 3.0 grams or even 2.0 grams given at one injection are usually associated with marked parathesias and other transitory nervous disturbances. Although patients may tolerate such sensory disturbances, if forewarned and assured of their harmlessness, it may be better to use doses devoid of even such causes of alarm.

Doses of 1.0 gram given once a week produced a definite therapeutic response in many patients, but failed in some others who later improved when given larger amounts. Doses of 2.0 or 3.0 grams, however, appeared to be just as effective as larger doses.

Intermittent regimens of 10 gram every three days or 20 grams once a week are now being followed in many institutions Dihydro-streptomycin has also been given in these dose schedules with similar response

The increased intervals are used chiefly in the hope that by this means the development of resistant forms of tubercle bacilli which are refractory to streptomycin may be delayed The limited data so far available, suggests that administration of streptomycin at intervals several days apart, or in repeated short daily courses with intervening rest periods, results in a prolongation of the total elapsed time before resistant forms appear

It is not necessary to give large toxic doses of streptomycin in the treatment of pulmonary tuberculosis and its complications Doses of 0.33 gram of streptomycin daily, 10 gram administered every three days, or 20 grams once a week are usually safe and effective If symptomatic response is not observed within two weeks following the starting of such dosage, or if relapse occurs after initial improvement during continuation of treatment, the dose may be increased but treatment should not be continued if the lack of beneficial effect is due to the development of streptomycin-resistant bacilli

Combinations of streptomycin with other bacteriostatic agents not only yield enhanced therapeutic effect, but result in a delay in the development of resistant forms Although the sulfones have proved effective in experimental animals and produce response in some patients, they are too toxic for general recommendation Para-aminosalicylic acid (PAS) is now available in this country and has proved both experimentally and clinically to have effect similar to that of streptomycin though perhaps somewhat less It is, moreover, effective in instances of infection with streptomycin-resistant organisms

Three grams of para-aminosalicylic acid with $1\frac{1}{2}$ grams of sodium bicarbonate and $1\frac{1}{2}$ grams of sugar freshly dissolved in a glass of water, may be given four times a day The PAS should be given at the same time as the streptomycin rather than at an earlier or later time in order to have the best effect on delay in the development of resistant forms It may be possible by giving PAS only a few days a week, coincident with the streptomycin to obtain this beneficial synergistic effect while still avoiding much of the gastrointestinal toxicity which accompanies many of the present-day preparations of PAS Treatment with PAS on the day of an intramuscular injection of streptomycin and on the following day only may be sufficient to secure this synergistic effect

Careful selection of the optimal time for administration giving the streptomycin intermittently with several days to a week inter-

val between doses, and combining streptomycin with para-aminosalicylic acid or other chemotherapeutic agent, and giving courses only long enough to obtain the desired result, will delay the development of resistant forms. It may be possible to secure the benefit of repeated courses of streptomycin chemotherapy as indications arise in the same patients before the development of streptomycin-resistant organisms renders such treatment futile. The indications for this treatment have been considerably extended and the objections to it greatly diminished by these measures so that the majority of patients suffering from active tuberculosis may now be considered potential candidates for modern chemotherapeutic measures.

SUMMARY

Streptomycin need not be administered in large amounts, four to eight daily doses, totalling 1 to 3 grams a day for three to six months, to elicit a favorable response in the treatment of tuberculosis. Such a frequent, heavy and prolonged regimen is likely to injure the patient and leads to the emergence of resistant organisms which render further use of this agent futile.

The minimal effective dose is about 0.2 grams a day, or 4 milligrams per Kg, and double this amount offers an adequate factor of safety. Two grams of streptomycin given only once a week or 1 gram twice a week, is not only less toxic, but is less rapidly followed by the development of resistant bacilli. Combinations of streptomycin with collapse therapy and with para-aminosalicylic acid, or other chemotherapeutic agents, still further conserve its efficacy and extend the indications for its use.

RESUMEN

Para producir una respuesta favorable en el tratamiento de la tuberculosis por la estreptomicina, no se necesita que esta sea administrada en grandes cantidades a las dosis de cuatro a ocho dosis diarias con un total de 1 a 3 gramos.

Tales dosis frecuentes y grandes son capaces de dañar al enfermo y conducir a la aparición de organismos resistentes y hacer su uso ineficaz.

La dosis mínima eficaz es alrededor de 0.2 por día o 4 miligramos por kilo de peso y el doble de esto proporciona un factor adecuado de seguridad.

Dos gramos de estreptomicina dados solamente una vez por semana es una dosis no solo menos tóxica sino menos rápidamente seguida por desarrollo de resistencia bacteriana. Las combinaciones de estreptomicina con colapsoterapia y con ácido para-aminosalicílico aun sirven para conservar su eficacia y para ampliar las indicaciones para su uso.

Streptomycin in the Treatment of Miliary and Meningeal Tuberculosis

Based on a Study of 30 Cases*

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Introduction

Whether acute hematogenous dissemination of tubercle bacilli results in miliary tuberculosis, tuberculous meningitis, or a combination of the two, the ensuing diseases, though very closely related etiologically, are nevertheless distinct clinical entities, each with a different prognosis and therapy.

The immediate mechanism, which is responsible for the infection assuming one or the other clinical form, is a matter of speculation and may be due to a variety of causes such as the anatomical position of the primary source of dissemination, the amount of infected material thrown into the circulation, the frequency of disseminations, possibly the vaguely understood individual variation in organ susceptibility, the patients' general resistance, or a combination of these and other causes. An answer to this question, which may supply the key to prevention and, perhaps, to more successful therapy, must await further study.

The reported results of treatment of acute disseminated tuberculosis with streptomycin have varied greatly. Only certain types of miliary disease (probably of a predominant local pulmonary type) have responded with any degree of permanent success.

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Reports of successful treatment in this type of disease vary roughly between 40 and 100 per cent. Uncomplicated meningitis has been reported as responding favorably in 20 to 75 per cent of cases, while combined military and meningeal disease has shown a variation from 5.5 to 58.5 per cent favorable results, depending chiefly on the time during which observation has been continued after treatment. If every case were followed for two to three years, the percentage of survivors would probably be reduced to half or less of the first reports. The degree of recovery has varied from a mere prolongation of life, to the production of various types of neurological "cripples," or to a temporary (or permanent) return to normal health. In general, the reported success has depended (besides the variation in types of disease mentioned) upon the age of the patient, the duration of the disease before the treatment was begun, possibly to a certain extent upon the method of treatment, and most important of all, upon the *length of time the patient was observed after the treatment was finished*.

Some of the more important studies will be reviewed. There are numerous single case reports of survivals, observed from several months to two years, including those of Cooke, Dumphy, and Blake,¹ Applebaum and Halkin,² Mehas and Tiuxax,³ Bauer and Sauer,⁴ and many others. Such reports are, however, of limited value. Larger groups of cases, with longer periods of observation after treatment, are necessary to permit any reliable conclusions.

Among the first hundred cases of all forms of tuberculosis treated by Hinshaw and his associates,⁵ 12 had military tuberculosis and/or meningitis. Five of these were alive at the time the report was made, but only three (25 per cent) have survived for three years.⁶

Cocchi and Pasquinucci⁷ reported in April 1947 on 28 cases of meningitis, for the most part in children, which had been treated between December 11, 1946 and April 11, 1947, 21 cases (73 per cent) survived. Obviously the time limit was too short for a worthwhile appraisal of results.

Debré, Thieffry, and Brissaud^{8,9} reported 43 survivors (46 per cent) amongst 93 cases of meningitis in children treated between September and December 1, 1947. Only 27 (29.1 per cent) of the cases, however, were in good condition and only 7 (8 per cent) entirely well at the time of their second report. The cases of acute military tuberculosis were especially noteworthy. Of 10 such cases, free from meningitis, eight were living (80 per cent), of 15 who had meningitis at the time treatment was begun, six were living (40 per cent), and of six with meningitis which developed *after* treatment was begun only one was alive (16.7 per cent). Debré, Brissaud, and Noufflard¹⁰ added seven more cases to the series.

(making 100 cases in all) with 46 cases (46 per cent) regarded as "cured" two to 10 months after treatment was finished

Decourt and his associates¹¹ treated 72 cases of meningitis during more than a year, at the end of which time only 13.9 per cent had sufficiently recovered so that treatment could be stopped, 33.3 per cent were still under treatment, 22.2 per cent who died had their lives prolonged for varying periods of time, and 30.5 per cent died without revealing any effect of the drug. He stated significantly that in no case could they describe any patient as *cured*.

Fouquet¹² treated 50 cases of "pure" (simple) meningitis and reported nine (18 per cent) were clinically "cured", eight (16 per cent) were in "good condition", thirteen (26 per cent) were still under treatment, four (8 per cent) had developed "chronic meningitis," and sixteen (32 per cent) were dead.

De Lavergne¹³ stated that "favorable" results could be expected in about 25 to 30 per cent of patients with tuberculous meningitis. Mouriquand¹⁴ reported that 24 (58.5 per cent) cases of "pure" meningitis were living out of 41 treated cases, and only one of four (25 per cent) patients with combined miliary-meningeal tuberculosis had survived.

Cathala and Bastin,¹⁵ in 41 cases of "pure" meningitis in children, reported that 17 (41.5 per cent) were living and 24 were dead. Of the living, 12 were still under treatment, among the five whose treatment was completed, only two were well. Of 21 cases of miliary tuberculosis, eight were dead, eight were still under treatment, and five had completed treatment, of the latter, only two were entirely well. Of 16 miliary-meningitis patients, seven (43.7 per cent) were living at the time of the report, four of whom were still under treatment and three in grave condition.

Sedallian and his associates¹⁶ reported that of 35 adult cases of miliary disease only six (17.1 per cent) were living. Etienne Bernard¹⁷ reported 20 (25.9 per cent) of 78 adult cases of meningitis to have survived at least eight months. In a later report by the same author,¹⁸ only 14 of the same cases (18 per cent) were alive after 14 months.

Van Goidsenhoven, Stevens and Crolla¹⁹ reported 21 (65.6 per cent) of 32 cases with generalized disease to be alive five to 12 months after treatment was started. Among other things they warn, that in spite of immediate improvement in a majority of cases, there should be the "greatest reserve" in making an ultimate prognosis for "at least a year after cessation of treatment."

Marshall and his associates²⁰ treated 105 cases of tuberculous meningitis in children, 30 of them (28 per cent) survived for a period of 120 days or more. In general the younger the children and the longer the disease had existed before treatment the worse

were the results. The work of these authors also seemed to indicate that the addition of some intrathecal medication was advantageous because of 72 cases receiving combined intramuscular and intrathecal administration, 25 (35 per cent) survived whereas only three (11 per cent) of 28 cases who received intramuscular treatment alone survived.

Löffler and Piotti²¹ observed 13 cases of meningitis in adults for about a year, three (23 per cent) survived. Life was believed to have been prolonged (in one instance for 328 days) in all fatal cases.

Lincoln, Kirmse and De Vito²² treated seven cases of meningitis. Six (85 per cent) survived for from two to eight months and only two had post-treatment complications.

Since most of the European reports were on children, the report of Bunn²³ from the Veterans Administration Hospitals has given the best available data on adults, and the cases have been followed longer than any others of which records are available to us. Out of 100 cases of military tuberculosis and/or meningitis, 24 (24 per cent) were alive 11 to 25 months after treatment was completed and 15 (15 per cent) were entirely well. Twelve (58.2 per cent) of 22 military cases, nine (20.9 per cent) of 43 cases of simple meningitis, and only three (8.5 per cent) of 35 cases of military-meningitis, were alive at the time the report was made.

The dosage which has been used in the treatment of generalized disease has been quite variable. With the exception of Van Goid-senhoven, who gave intrathecal treatment prophylactically, no intrathecal treatment was given if the military tuberculosis occurred without meningitis. Most investigators who have compared combined intrathecal and intramuscular therapy with intramuscular alone in the treatment of meningitis, have been unalterably in favor of the former regimen.

It would require much discussion to outline the various regimens which have been used. In general, they may be divided into large, medium, and small dosages, both intrathecally and intramuscularly, and in many instances each category has been supplemented with adjuvant drugs, such as the sulphones, vitamins A, B, and D, and with surgery.^{10, 24}

The duration of intramuscular treatment has varied from three to eight months. Intrathecal injections have been given with varying frequency (daily to weekly) over various periods of time, and interrupted courses (one week on and two weeks off) have been used. Some authors varied the treatment with practically every patient.

The intramuscular dosage varied from a total of 2 gm a day down to 0.1 gm a day and has usually been given in six to eight

equally divided doses The intrathecal dosage ranged from 0.1 to 0.2 gm to as low as 0.015 gm a day Recently, there has been a tendency to use smaller dosage and, especially, fewer and more widely spaced intrathecal injections

Analysis of Clinical Material and Results of Treatment

From January 1, 1947 to April 15, 1949, 1212 patients, all adult males, were treated on the Tuberculosis Service of this hospital Thirty of these patients were either admitted for, or have subsequently developed, one or another form of the military-meningeal group of diseases

The present report is based on a study of these 30 cases They are divisible as follows Nine cases of military tuberculosis, 14 of tuberculous meningitis, and seven of tuberculous meningitis superimposed on military tuberculosis (Table 1)

Treatment Regimens

Military Tuberculosis The first two patients were treated with 1 gm of streptomycin intramuscularly for 111 and 120 days respectively and the third, a terminal case, received 2 gm daily and survived only seven days Subsequent to this, all patients with military tuberculosis were placed on a regimen of 1 gm of streptomycin intramuscularly, with the addition of 4 gm of promin intravenously, daily, for 120 days Promin was omitted every third week of therapy When meningitis was recognized in a patient under treatment for military tuberculosis, his treatment was changed to the combined military-meningeal regimen (see below)

Tuberculous Meningitis The first four patients were placed on a regimen of 1.8 to 2 gm of streptomycin intramuscularly, daily, and 0.05 gm of streptomycin intraspinally three times per week for 120 days The remaining 10 patients were placed on a regimen of 2 gm of streptomycin intramuscularly and 4 gm of promin intravenously, daily, and 0.05 gm of streptomycin intraspinally

TABLE 1
Results in All Types of Military and Meningeal Tuberculosis

	Died During RY	Died After RY	Survived to Present	Total
Military alone	3*	0	6 (66.7%)	9
Meningitis alone	7	4	3 (21.4%)	14
Military-meningitis	6	0	1 (14.3%)	7
TOTAL	16	4	10 (33.3%)	30

*Terminal state on admission

three times per week, for 120 days Promin was omitted every third week of therapy Intraspinal therapy was omitted in four patients (7, 8, 12 and 14)

Combined Miliary-Meningeal Tuberculosis The seven patients in this group received treatment similar to those with meningitis alone, except that intramuscular streptomycin was increased to 4 gm per day for the first two weeks and then reduced to 3 gm per day for the remainder of the treatment period

Miliary Tuberculosis

During the period covered by this report, nine patients received streptomycin therapy for miliary tuberculosis alone (Table 2) Their ages ranged from 22 to 54 years Eight of the nine patients were Negroes Taking into consideration the usual proportion of Negro to white patients on our wards, the incidence of miliary tuberculosis was about 28 times greater in the Negro than in the white patients

The estimated duration of symptoms suggestive of miliary tuberculosis before treatment was started, ranged from one to 18 weeks The vast majority of patients were acutely ill and their temperatures ranged from 101 to 104 degrees F Shortness of breath was a common complaint Comparable roentgenograms were not available in three patients (Table 2) who were in terminal state and died on the 7th, 10th and 37th day of therapy respectively and

TABLE 2
Miliary Tuberculosis — Treated Before April 15, 1949

Case No	Name	Age	Race	Sympt Pre-RX (Wks)	Duration of RX (Days)	X-Ray 1st Noted (Wks)	Changes Degree of Improv	STATUS 4 15-49 Living (Days*) Dead (Days*)
1	R S	27	C	16	111	6	Mkd	111**
2	R J	51	C	1	120	12	Mod	524
3	W H	22	C	4	7			7
4	N L	23	W	4	120	8	Mkd	453
5	R B	42	C	2	37			37
6	J B	54	C	2	120	8	Mkd	365
7	T W	38	C	1	10			10
8	J M	34	C	18	120	4	Clear	358
9	H M	31	C	16	120	4	Mkd	191

*Days after first starting treatment for miliary tuberculosis

**AWOL on the 111th day and lost to study Reported to be alive April 30, 1949

could not be x-rayed. In the remaining six patients, the roentgenograms revealed marked to complete clearing in five patients and moderate clearing in one. Improvement was often noted six weeks after starting treatment and was observed on all two-month films, but continued through and following the treatment period of 120 days. One patient left the hospital of his own accord twice during the height of his illness and returned, and though his miliary dissemination showed moderate clearing he developed progressive pulmonary tuberculosis and his prognosis is poor.

TABLE 3
Tuberculous Meningitis — Treated Before April 15, 1949

Case No	Name	Age	Race	Duration Sympt Pre RX (Wks)	Assoc Tb Cond	Duration of RX (Days)	STATUS 4-15 49	
							Living (Days1)	Dead (Days1)
1	W L	58	C	0 5	Pul	63		63
2	E F	23	W	12	Pul	120		259
3	W K	29	W	1 5	Ankle	120 ¹ 62 ² 75 ²		354
4	J A	54	W	4 5	Pul	120 ³ 42 ³		188
5	J M	29	C	2	Adenitis	66		164
6	F McC	23	W	2	Pul	120	426	
7	P T	30	W	2	Pul Empty	98		151
8	F M	38	W	1 5	Pul	120		161
9	W W	50	C	4	Pul	10		10
10	E J	53	C	2		28		28
11	J M J	29	W	1	Pl Effus	7		7
12	J C	29	W	2	Adenitis	180 ⁴	180	
13	L V W	56	C	2	Pul Larynx	1		1
14	W O D	19	C	6	Adenitis	120	177	

¹Days after first starting streptomycin treatment for tuberculous meningitis

²Relapsed one month after first course, retreated with streptomycin plus promin for 62 days, improved, relapsed again three weeks later, retreated 75 days without benefit and died

³Relapsed three weeks after first course and retreated with streptomycin plus promin for 42 days

⁴Treated an extra two months

Tuberculous Meningitis

During the period under discussion 14 patients had tuberculous meningitis, without miliary tuberculosis, and all were treated with streptomycin (Table 3). Their ages ranged from 19 to 58 years. Six were Negroes and eight were white. The incidence of tuberculous meningitis was about three times greater in the Negro than in the white patients. Five patients (5, 7, 8, 12 and 13) developed meningitis during or shortly after a course of streptomycin for other tuberculous conditions.

Of the 14 patients, 11 died and three survived to the date of this report. Four patients (9, 10, 11 and 13) died between the first and twenty-eighth day of therapy, and were not treated long enough to contribute significant data to Table 4. Three patients (6, 12 and 14) were alive six to 14 months after the beginning of therapy and had no symptoms referable to the central nervous system, although some residual abnormalities of the cerebrospinal fluid persisted (see Table 4 and Case Report 1).

Intraspinal therapy was omitted in four patients and two were alive six months after the start of treatment. Streptomycin was given intraspinally in 10 patients and one was alive 14 months after the start of therapy.

Symptoms. Headache was the earliest symptom suggestive of meningitis and was present in all patients. It was usually intermittent at first, becoming more and more constant as the disease progressed. Symptoms referable to the central nervous system varied in severity from headache through confusion or restlessness to drowsiness, stupor, and coma. Defervescence of fever, for varying periods of time, was noted in all patients.

Symptoms referable to the central nervous system were not improved in the four patients who died on the first, seventh, tenth and twenty-eighth day of therapy. The remaining 10 patients were treated two months or more and all but one (No. 7) showed at least temporary improvement of cerebral symptoms to a moderate or marked degree. This improvement was sustained from three to 14 months in six patients and two relapsed and died 259 and 354 days respectively after the beginning of treatment.

Neurological Findings. Nuchal rigidity was the earliest neurological finding in most cases and this rarely improved for more than a few days. This sign was absent throughout in one patient (No. 6). Kernig, Brudzinski, and/or Babinski reflexes were observed intermittently in 11 of the 14 cases. Absence of abdominal or cremasteric reflexes were noted in nine cases.

Of the 10 patients treated more than 28 days nine developed various paralyses with only one (No. 12) surviving to date, and

eight developed bladder or bowel incontinence with one survival (No 14)

Cerebrospinal Fluid (Table 4) Four of the more significant cerebrospinal fluid elements were selected and recorded. Four patients were treated less than 30 days and were therefore omitted from this table since they did not contribute significant data for discussion.

Accepting 150 mm as the upper limit of normal spinal fluid pressure in the lateral recumbent position, it was elevated in all patients at one time or another before therapy. During treatment, some lowering of pressure was recorded in seven of the 10 patients, it reached zero in one patient (No 4) and was associated with spinal block, paraplegia, and bladder and bowel incontinence.

The protein content was elevated before treatment in most of the cases. During treatment it increased further in seven of the 10 cases. In several patients it remained extremely high while the cell count was diminishing, the sugar level rising, and the clinical condition improving.

The sugar content was less than 50 mg in seven instances before treatment. During treatment the sugar level rose in nine and fell again as relapses occurred. On the whole, the sugar content followed closely other evidences of improvement or relapse.

The total cell count was elevated in all cases on at least one examination before treatment. During treatment it fell for some period of time in most cases and was in fair agreement with the clinical course.

Combined Miliary-Meningeal Tuberculosis

During the period covered by this report, meningitis was diagnosed on the 18th to 80th day of therapy for miliary tuberculosis in six patients. The seventh patient (No 2) received 0.5 gm of streptomycin for tuberculous laryngitis for 59 days before tuberculous meningitis and miliary tuberculosis were recognized (Table 5). Their ages ranged from 25 to 63 years. Five patients were Negroes and two were white. The incidence of combined miliary-meningeal tuberculosis in Negro patients was about nine times that in white. Temperatures tended to reach higher levels in this group than in the group with meningitis alone. Temporary response to streptomycin therapy occurred in all but was sustained in only one patient.

Of the seven patients, six died and one survived to date of this report (see Case Report No 2). Of the six who died, four showed temporary improvement of symptoms referable to the central nervous system. The abnormal neurological findings in this group

TABLE 4—Cerebrospinal Fluid Findings (Tuberculous Meningitis)

Case No	Name	Pre-RX	DAYS AFTER START OF STREPTOMYCIN										Diag Conf by
			0-15	15-30	30-60	60-90	90-120	120-180	180-240	240-300	300-360		
1	W L	Pres 300 mm Prot 185 mg Sugar 33 mg Cells 75	215 41 84	230 325 57 256	360 100	Died						Sx 6 Cx 2	
2	E F	Pres 200 mm Prot 850 Sugar 55 mg Cells 207	120 850 42 159	90 950 59 84	180 65 19	70 15 222	Died					S	
3	W K	Pres 480 mm Prot 100 mg Sugar 37 mg Cells 286	280 71 37 5 37	260 165 15 14	200 185 37 16		310 58 40 700	260 300 54 116	Died			Sx 2 Cx 6	
4	J A	Pres 290 mm Prot 49 mg Sugar 30 mg Cells 200	120 55 340	85 195 34 73	70 55 23		80 350 25 86	Died 145 50 4 40				Sx 1 Cx 3 P M	
5	J M	Pres 130 mm Prot 300 mg Sugar 30 mg Cells 78	370 820 69 18	200 400 66 14	370 800 75 12		140 114 47 14	Died				C P M	
6	F McC *	Pres 200 mm Prot 492 mg Sugar 30 mg Cells 66	250 355 20 296	250 495 20 386	170 400 41 96		180 594 50 228	140 212 63 28	120 121 60 34	140 100 66 2		GP	
7	P T	Pres 200 mm Prot 126 mg Sugar 52.3 mg Cells 174	265 130 43 5 1026	65 40 30	240 92 5 31 2	Died						P M	
8	F M	Pres 330 mm Prot 140 mg Sugar 37.5 mg		205 325 40 24	220 500 192		70 1000 50 10	Died				P M	

MILIARY AND MENINGEAL TUBERCULOSIS

Volume XVI

Case No	W M C *	Hb			RBC			WBC			Living	C x 2 G P	All conf
		100 mm	200 mm	300 mm	100 mm	200 mm	300 mm	100 mm	200 mm	300 mm			
9	W W	14.0	14.0	14.0	10.0	10.0	10.0	10.0	10.0	10.0	130		
10	E J J	14.0	14.0	14.0	10.0	10.0	10.0	10.0	10.0	10.0	181		
11	J M J	14.0	14.0	14.0	10.0	10.0	10.0	10.0	10.0	10.0	83		
12	J F C	14.0	14.0	14.0	10.0	10.0	10.0	10.0	10.0	10.0	4		
Treated for meningitis from 1 to 28 days and supplied no significant data for this table													
		600	450	330	130	120	130	130	120	130	130		
		163	360	550	520	440	520	440	460	520	4		
		72	70	74	211	69	211	69	46	211			
		134	118										
13	L V W	Pres 190 mg Prot 54 mg Sugar 520 Cells	240	150	200	170	302	170	495	70	24		Not conf
Treated for meningitis one day and supplied no significant data for this table													
		160	725	45	8	47	24	45	8	12			
		175	700	40	12								
		48	132	36									
14	W O D	Pres 424 mg Prot 245 mg Prot 36 mg Sugar 348 Cells	240	150	200	170	302	170	495	70	24		
Treated for meningitis one day and supplied no significant data for this table													
		160	725	45	8	47	24	45	8	12			
		175	700	40	12								
		48	132	36									

*See Case Report No 1 for latest findings

TABLE 5
Combined Military-Meningeal Tuberculosis
(Treated Before April 15, 1949)

Case No	Name	Age	Race	Sympt Pre RX (Wks)		For Mil Mts (Days)	Total RX (Days)	1st Noted (Wks)	Degree of Improv	X RAY CHANGES	STATUS 4-15 49 Living (Days*) Dead (Days*)
				Sympt Pre RX (Wks)	For Mil Mts (Days)						
1	TS	29	C	6	80	1	149	88	128	9	Mod
2	FH	48	W	2	61	85	240	120	128	5	Mkd
3	CL	29	C	10	35	10	28	10	60	8	Mkd
4	JJ	40	C	3	18	55	81	42	121	6	Unchg
5	AW	63	W	3	39	42	81	42	121	6	Mkd
6	JK	32	C	3	39	42	81	42	121	6	Unchg
7	JS	25	C	3	39	42	81	42	121	6	Mkd

*Days after streptomycin was first started

*Days after streptomycin was first started

were similar to those in the group of patients with tuberculous meningitis alone

Roentgenological Changes (Table 5) One patient died 28 days after treatment for miliary tuberculosis was started and there were no x-rays available for comparison. In the remaining six patients, there was marked to complete clearing in four (66.7 per cent), moderate clearing in one, and no change in one. It should be noted that there was marked clearing in the x-ray of one patient (No. 2), previously mentioned, who was treated for 59 days on a daily dosage of 0.5 gm streptomycin for tuberculous laryngitis before miliary tuberculosis and tuberculous meningitis were recognized.

Cerebrospinal Fluid (Table 6) Two patients, who died on the first and 10th day of therapy respectively, did not supply sufficient data to be included in Table 6. Prior to therapy, the spinal fluid pressure was elevated in all cases except one (No. 7). The protein content and the cell count were elevated and sugar was lowered in all cases before therapy. Only one patient (No. 4) showed definite and sustained improvement in all elements during and since treatment ended (see Case Report No. 2).

One patient (No. 7), who was under streptomycin treatment for miliary tuberculosis, revealed tubercle bacilli on culture of a specimen of cerebrospinal fluid in which no other abnormal elements were found. This specimen was obtained during a routine spinal tap at a time when no symptoms suggestive of tuberculous meningitis were apparent. Two weeks after the tap was performed, the patient developed headache—the first symptom suggestive of meningitis. Treatment was changed to the miliary-meningeal regimen. The patient died six weeks later and necropsy confirmed the clinical diagnosis. This case demonstrates the long incubation period of tuberculous meningitis. The two patients who survived more than 14 months will now be described in greater detail.

Case No. 1 F McC, Reg. No. 203 452 (No. 6 on Tables 3 and 4), a 23 year old white male was admitted February 2, 1948 with a diagnosis of far advanced pulmonary tuberculosis with multiple cavities and hyperactive deep reflexes. Spinal tap revealed the cerebrospinal fluid under pressure of 200 mm with protein 492 mg, sugar 30 mg, cells 66 per cc (lymphocytes 80 per cent, neutrophils 20 per cent) chlorides 656 mg. No tubercle bacilli were found on smear, culture, or guinea pig inoculation.

He received 2.0 gm streptomycin intramuscularly daily 0.05 gm intraspinally three times per week, and 4.0 gm promin intravenously daily from February 4, 1948 to June 3, 1948. Promin was omitted every third week. His temperature dropped to normal. Headache and nuchal rigidity disappeared. The diagnosis was confirmed by inoculation of a guinea pig with cerebrospinal fluid taken two months after cessation of therapy. During the second month of therapy pain and weakness of the right lower extremity appeared and this cleared completely two months later.

This patient was clinically well 14 months after the beginning or 10 months after the termination of therapy. A specimen of cerebrospinal fluid obtained April 4, 1949, 10 months after completion of treatment, revealed the following: pressure 130 mm, proteins 68 mg, sugar 87 mg, cells 6 (lymphocytes), chlorides 715 mg. Tubercle bacilli were not found on the last eight monthly examinations. All specimens were examined by smear, culture, and guinea pig inoculation.

Case No 2 J J, Reg No 202 563 (No 4 on Tables 5 and 6), a 39 year old Negro was admitted on January 24, 1948, acutely ill, with a temperature of 102 degrees F. X-ray film of the chest revealed generalized



FIGURE 1a Extensive miliary seeding at beginning of streptomycin therapy. This was followed by tuberculous meningitis 35 days later when treatment was changed to the miliary-meningitis regimen.

miliary tuberculosis (Fig 1) He received 1 gm streptomycin intramuscularly and 4 gm promin intravenously, daily, omitting promin every third week, until tuberculous meningitis was diagnosed on the 35th day of therapy, at which time treatment was changed to the miliary-meningeal regimen and continued for the remainder of 120 days This resulted in complete clearing of the pulmonary dissemination by the fifth month of therapy and disappearance of all symptoms and neurological findings suggestive of meningitis (Table 6) Relapse of meningeal symptoms occurred two months after termination of his first course of treatment and he was retreated for four months on the meningitis regimen (not on the combined miliary-meningeal regimen) He quickly responded to



JJ I 20 49

FIGURE 1b Continuous clearing of pulmonary lesions has taken place simultaneously with the appearance of symptoms of meningitis followed successively by remission, relapse and remission again on retreatment

retreatment and was clinically well and free of symptoms 14 months after the beginning of treatment or five months after termination of retreatment

A specimen of cerebrospinal fluid obtained March 24, 1949, five months after termination of retreatment, revealed the following pressure 125 mm, protein 100 mg, sugar 87 mg, cells 0, chlorides 718 mg. Tubercle bacilli were not recovered on numerous examinations during the past eight months

Discussion

Due to the acute nature of miliary tuberculosis and its rapid evolution, the general symptoms usually dominate the clinical picture and the true nature of the disease may not be discovered until quite late. A considerable number of such patients are therefore apt to reach the tuberculosis ward in an almost moribund state. The three deaths in this group of nine patients occurred within 37 days after beginning of therapy and there were no late deaths (Tables 1 and 2)

Quite a different picture is presented by the meningeal cases. Of the 14 patients with meningitis alone (Table 3), 11 died and the three survivors still have abnormal cerebrospinal fluids and are considered in remission. Of the seven patients with combined miliary-meningeal tuberculosis, six died and one is living 14 months after beginning of therapy (Table 5). He is free of symptoms but his cerebrospinal fluid is still abnormal (Case Report No. 2)

Our early enthusiasm concerning the value of streptomycin in the treatment of tuberculous meningitis was considerably dampened as one after another of the patients who were apparently on their way to recovery ceased responding to the drug, gradually lapsed into coma or developed some complications, and died. And, judging by our own experiences, the same fate was probably met by many of the cases reported as cures in the literature.

Yet, regardless of the paucity of permanent and complete recoveries, the value of this drug against tuberculous meningitis should not be underestimated. Rather, we must search for means of enhancing its action. In our disappointment over relapses in the majority of cases treated, we are liable to lose sight of the fact that we are dealing with a disease which was heretofore 100 per cent fatal in about two to eight weeks, and in which remissions were practically unknown. Notwithstanding the eventual fatal issue, the favorable early therapeutic response and the unprecedented survival for many months, to more than a year in many cases, are in themselves great achievements and prove the effectiveness of the drug up to a certain point. One must now look for the reason why streptomycin, which is so effective a therapeutic agent against tuberculous meningitis at first, fails eventually

in most of the cases. Somewhere along the line streptomycin loses its potency. At what point does this change take place, and why?

Bacterial resistance undoubtedly plays its role in limiting the effectiveness of streptomycin in tuberculous meningitis, but, presumably, to no greater extent than it does in other forms of tuberculosis. It is natural to suspect, then, that the condition which limits the effectiveness of the drug in this type of tuberculosis may lie not in the bacterial agent but may be inherent in the normal and pathological anatomy of the organ involved.

Particularly impressive are the following facts: (a) no recurrence of pulmonary seeding was observed in any of our miliary cases, (b) no pulmonary seeding was observed in any of our patients who developed tuberculous meningitis first, (c) none of our patients with uncomplicated miliary tuberculosis died of this disease if he survived six weeks under streptomycin therapy, (d) none of our patients with miliary tuberculosis developed meningitis if he did not exhibit symptoms of meningitis during the first two months of streptomycin therapy, and (e) clearing of the miliary lesions, from moderate to complete, was observed, regardless of streptomycin dosage, in five of six patients with combined miliary-meningeal disease who survived long enough to be x-rayed 42 days after beginning of streptomycin therapy, even though the meningitis proved fatal in all but one patient.

How shall we account for the marked effectiveness of the drug to apparently control the lesions in the lungs and the apparent ineffectiveness to accomplish the same purpose in the central nervous system? How shall we explain the freedom from relapses in the lungs and the frequent relapses in the central nervous system? If successive seedings are responsible for relapses in meningitis, why should the lungs have uniformly escaped reseeded? What role, if any, do successive seedings play in the occurrence of relapses? Our knowledge of the action of streptomycin and of its effect on different types of tuberculous lesions leads us to believe that when streptomycin fails to materially benefit a tuberculous lesion in a patient, who is not moribund, and whose organisms are not resistant, it is frequently due to the inability of the drug to make effective contact with the tubercle bacilli. The answer to these perplexing questions may possibly be found, to some extent, in different sources of dissemination with different degrees of accessibility of the tubercle bacilli to the action of this antibiotic.

Zollinger,²⁵ in his report of 22 necropsies, observed evidence of sclerosing meningitis in cases of "subacute and chronic" tuberculous meningitis treated with streptomycin. On the other hand, Baggenstoss, Feldman, and Hinshaw²⁶ emphasize the fact that they

observed no evidence of healing in the hematogenous lesions of the brain in four patients who died of miliary-meningeal tuberculosis, although there was definite evidence of healing in the miliary tubercles of the lungs, liver, and spleen. These authors further note that, when the concentration of streptomycin was determined in various tissues and body fluids in one of their cases which came to autopsy, a considerable amount of the drug was found in all specimens examined except the brain, and although 15.8 mcg per ml was found in the spinal fluid, no streptomycin was detected in the brain tissue. Adcock and Hettig²⁷ reported finding no streptomycin in the brain and liver in one case of tuberculous meningitis treated with streptomycin and a trace in another case, while finding appreciable amounts of the drug in other tissues and body fluids.

Pursuing the same line of investigation, Wallace and his co-workers²⁸ studied the effects of adding streptomycin in equal amounts to three different culture media, one of which consisted of a brain-heart infusion. They found that *Eberthella typhosa* and *Staphylococcus aureus* grew well in the brain-heart infusion, but decreased in number in the other cultures, thus suggesting that there is something in the brain-heart infusion which has the property of rendering streptomycin ineffective.

Continuing further on the trail of the streptomycin inhibiting factor, Rhymer and Wallace²⁹ located it finally in a brain infusion from which they apparently succeeded in extracting it. Since brain tissue is thus shown to possess antistreptomycin activity *in vitro*, it is logical to suspect that something else than the hematoencephalic barrier may account for the absence of streptomycin in the brain when it was present in other organs.^{26, 27}

Whether a particular case of meningitis is due to hematogenous seeding of the meninges or to direct extension from a cortical caseous focus or, possibly, to seeding from a focus elsewhere in the body, it is always secondary to an older caseous focus.

Certain pathological and clinical evidences suggest the probability that streptomycin may not penetrate to a significant extent into the larger caseous masses: (a) this drug is usually most effective on surface lesions where necrotic material easily separates and is cast off, (b) it seems least effective on tuberculous lesions of internal organs where large caseous masses remain locked up for a considerable time or indefinitely, (c) this antibiotic has a profound effect on miliary tuberculosis where individual areas of caseation, if present, are minute and are apparently more accessible to the drug than the larger ones, (d) streptomycin is carried through the blood stream and there is no blood supply to the caseous masses.

If it is true that streptomycin does not penetrate the avascular necrotic mass of the caseous tubercle in effective concentration, the tubercle bacilli usually found in such lesions would be comparatively safe from the action of this antibiotic. The greater the area of caseation, the safer are probably the tubercle bacilli within it.²⁶ And, when the caseous focus happens to be located in the brain, the tubercle bacilli within may have a double defense the caseous mass as well as the antistreptomycin factor in the brain tissue.

If this hypothesis is correct, more effective therapy of tuberculous meningitis would depend primarily, upon devising means for overcoming the antistreptomycin factor in the brain and, secondarily, upon finding a way of carrying the drug into the caseous foci in therapeutic concentration. Attempts to overcome these obstacles have been made and a ray of hope is visible.

Nelson and his co-workers³⁰ have shown that streptomycin mixed with trypan blue and injected into guinea pigs was retained in the liver and spleen in appreciable quantities as long as 25 hours after the injection. On the other hand, when streptomycin unmixed with trypan blue was injected into guinea pigs, a small amount of it was found in the liver one hour after injection, but no streptomycin was detected in this organ four hours after, or in the spleen at any time. However, Bogen's³¹ attempt to treat tuberculous guinea pigs using streptomycin mixed with trypan blue produced entirely negative results.

Based on the work of Jobling and Petersen,³² who showed that iodine is able to bring about the liquifaction of caseous material and the subsequent liberation of tubercle bacilli held within it, Woody and Avery³³ treated one group of tuberculous guinea pigs with streptomycin alone and another group with both streptomycin and potassium iodide. They found that the mortality in the two groups at the end of 12 weeks of treatment was six out of 13 with streptomycin alone and two out of 14 with streptomycin and potassium iodide.

The use of streptomycin in combination with streptokinase has considerably improved the results from the treatment of tuberculous meningitis in the experience of Cathie³⁴ who states that streptokinase helps to bring about lysis of the fibrin clots, frequently found at the base of the brain in patients who died of tuberculous meningitis, and thereby enables the streptomycin to make contact with the, usually, sensitive organisms found in these clots. In two small groups of patients treated, the recovery rate was 21 per cent with streptomycin alone and 58 per cent with streptomycin and streptokinase combined.

Experience with the use of streptomycin in the treatment of

various forms of tuberculosis³⁵ has given ample proof that if this drug is effective at all it is usually as effective with 1 gm as it is with higher doses. Our own studies reveal that 1 gm streptomycin is highly effective in military tuberculosis. The multiplicity of regimens employed in the treatment of tuberculous meningitis, the apparent lack of a consensus as to what constitutes the optimum regimen, an analysis of the reported results, as well as our own observations, seem to indicate that, with the possible exception of intrathecal medication, the effects of therapy in this disease have heretofore not varied conspicuously with the different dosages of streptomycin generally employed, whether alone, or in combination with other drugs. It may therefore appear futile to expect better results than heretofore by continuing the attacks on tuberculous meningitis with higher doses of streptomycin. Until another and more effective antibiotic against tuberculosis is discovered, we should change our mode of attack on this problem and aim our efforts primarily at finding means of penetrating more effectively the defenses behind which the tubercle bacilli may find protection in the human body. We must enable the drug to make adequate contact with the organism wherever it may be. The experiments with trypan blue, iodides, and with streptokinase seem to be steps in the right direction.

It seems likely that the cases of tuberculous meningitis in which an apparently permanent cure is obtained may have originated from a tuberculous focus outside the brain wherein the tubercle bacilli have possibly only one line of defense—the caseous mass. On the other hand, the majority of cases, the ones that succumb to the disease sooner or later, may have been caused by lesions in the brain where the organisms have possibly a fairly effective double defense system. The initial remission of symptoms in these cases could be due to the ready contact streptomycin is able to make with the tubercle bacilli in the more accessible areas and organs involved, all of which play their respective parts in contributing to the overall clinical picture.

SUMMARY AND CONCLUSIONS

1) Streptomycin seems effective in the treatment of uncomplicated cases of military tuberculosis. This could be accounted for by the small size of the individual tubercle which may permit the drug to readily penetrate throughout the lesion in therapeutic concentration and to come in direct contact with all the organisms, a condition which probably does not exist where larger areas of caseation are present.

2) Streptomycin did not prevent the development of tubercu-

lous meningitis in patients while they were under treatment with the same drug for other tuberculous conditions

3) It seems possible that the main obstacles to successful therapy of tuberculous meningitis may be (a) a factor in the brain, presumably, yet unidentified, which has the property of inhibiting streptomycin and thus rendering it ineffective, and (b) the relative inability of streptomycin to penetrate the larger caseous foci

4) Until a more effective antibacterial agent against tuberculosis may be discovered, efforts will undoubtedly be continued to identify the streptomycin inhibiting factor in the brain, and to find means of combating it. Further search is also indicated for some means of more effectively carrying the therapeutic agent into the caseous masses

5) Our experiences thus far lead us to believe that higher doses of streptomycin would probably not materially improve the results in tuberculous meningitis and in combined miliary and meningeal tuberculosis. It does not seem likely that the streptomycin inhibiting factor in the brain and the conditions which seem to prevent the drug from entering the caseo-necrotic mass in therapeutic concentration, could be overcome with relative safety by sheer volume of this antibiotic

Acknowledgment Grateful acknowledgment is made to Dr. Arthur M. Walker, Secretary of the Veterans Administration Central Office Streptomycin Committee, who kindly reviewed our manuscript and made many helpful suggestions

RESUMEN Y CONCLUSIONES

1) La estreptomicina parece efectiva en los casos de tuberculosis miliar no complicados. Esto puede atribuirse al pequeño tamaño del tubérculo individual lo que puede permitir a la droga penetrar a través de la lesión en un grado de concentración terapéutica y ponerse en contacto con todos los germenés, lo que probablemente no ocurre cuando hay áreas de caseificación

2) La estreptomicina no evitó el desarrollo de la meningitis tuberculosa en enfermos que estaban bajo el tratamiento con estreptomicina por otras localizaciones tuberculosas

3) Parece que los obstáculos más importantes para el tratamiento efectivo de la meningitis tuberculosa pueden ser (a) un factor en el cerebro probablemente aun no identificado que tiene la propiedad de inhibir la estreptomicina convirtiéndola en ineficaz, y (b) la relativa incapacidad de la estreptomicina para penetrar dentro de los focos caseosos más grandes

4) Mientras no se encuentre otro agente antibacteriano más eficaz contra la tuberculosis, sin duda que continuaran los esfuerzos para identificar el agente inhibidor en el cerebro y para

encontrar el modo de contrarrestarlo También se requieren medios para introducir mas eficazmente el agente en los focos caseosos

5) Hasta ahora nuestra experiencia nos conduce a pensar que las dosis más altas de estreptomycin no mejorarían materialmente los resultados en la meningitis tuberculosa y en la combinación de tuberculosis miliar y meningitis

No parece posible que el factor inhibiente cerebral y las condiciones que evitan el acceso de la estreptomycin dentro de las masas caseonecroticas pueda dominarse mediante gran aumento de volumen del antibiótico

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D i s c u s s i o n

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The experience in our department under the supervision of Dr Robert High has been similar to that of Dr Shamaskin and his group Dr High has had approximately two-thirds the number of patients (infants and children) under treatment reported in this series by Dr Shamaskin, but there is no significant difference in the results To the best of my knowledge, these results reflect the experience of other investigators now working in this country with the exception of Edith Lincoln at Bellevue Hospital Her results, reported recently before the American Pediatric Society, are better than those obtained in other clinics The reasons for the more favorable results in her series are not apparent While there are certain differences in her plan of therapy as compared with that of others, these would not appear to be significant Her ther-

apeutic regime includes 1 gram of streptomycin per day intramuscularly for a period of six months, 100 mgms of streptomycin intrathecally for 40 daily doses for 40 days (sometimes 50 mg every other day for 40 doses), and promizole over a period of three years. The plan of therapy now employed by Dr. High in conjunction with several other clinics who are cooperating in a study under the auspices of the Tuberculosis Control Division of the U. S. Public Health Service is as follows: 50 mgms of streptomycin per Kg. of body weight every 12 hours, promizole, 1 gram per day to infants under six months and 2 grams per day to patients over six months of age. In addition to these two agents, alternate cases receive 0.2 gm./Kg. of body weight per day of para-aminosalicylic acid. Streptomycin is administered for a period of six weeks with a rest period of 10 days, and repetition if there is still any evidence of tuberculous activity. Promizole and para-aminosalicylic acid are continued for a period of six months. The principal differences in relation to Dr. Lincoln's plan are: (1) She administers streptomycin for a period of six months, (2) Promizole, over a period of three years, and (3) she does not use para-aminosalicylic acid. There is no essential difference in the total daily dosage of streptomycin that is employed by the two groups. The principal difference would appear to be in the length of time that she continues Promizole. However, since most of the deaths in our clinic have occurred during the course of therapy this would not appear to be a deciding factor. Since most of her patients come from her own Out-Patient Dispensary it may be that treatment is started materially earlier in the course of the disease than it has been in other clinics such as ours where practically all of the cases are referred and at a time when the disease is well advanced.

It has been suggested but not proved that promizole may retard the development of resistance of the tubercle bacillus to streptomycin. At the moment we do not have data pertinent to this question but in one instance marked increase in the resistance of the tubercle bacillus to streptomycin was observed in a child who was receiving diazone in conjunction with streptomycin for the therapy of military tuberculosis and tuberculous meningitis. In the initial episode when there was an apparent remission of both the pulmonary and meningeal lesions, the tubercle bacilli were susceptible to streptomycin, subsequently during an exacerbation of the meningitis, from which the child died, the tubercle bacilli were quite resistant. The use of adjunct substances to enhance the effectiveness of streptomycin would seem to be the most likely possibility of an improvement in therapy at the moment. Our experience with para-aminosalicylic acid in this relation does not permit critical evaluation but it seems doubtful that it will

make any significant difference in the treatment of tuberculous meningitis

A search for substances which would materially enhance the effect of streptomycin in nervous tissue would seem to be important on the basis of present leads. Whether iodides will have a significant effect in making tubercle bacilli available from caseous foci is yet to be demonstrated, but is worthy of further investigation. The availability of a substance which would retard development of resistance by tubercle bacilli to streptomycin would seem to be an essential feature of long continued streptomycin therapy. While antibiotics more effective than streptomycin, e g, neomycin, against tubercle bacilli may be forthcoming, the problem of reaching tubercle bacilli implanted in non-vascular caseous foci remains a factor of first importance.

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I want to emphasize Dr Shamaskin's statement that age of the patient, duration of the disease, method of treatment and period of post therapy observation are factors which influence the results of the treatment of tuberculous meningitis with streptomycin. There is still, however, no clear-cut pattern of these influences and still no uniformity of opinion concerning the use of intrathecal therapy, the amount of drug to be used or the duration.

To add to this picture, and I hope not confuse it further, I should like to present data gathered from the use of streptomycin in the treatment of tuberculous meningitis in Detroit. For these statistics I am indebted to Dr Donald C Young of Herman Kiefer Hospital and Dr Edna M Jones of Maybury Sanatorium.

Slide Descriptions

Slide I shows that of 84 cases—61 or 73 per cent expired and 23 or 27 per cent recovered. The highest rates of deaths were among whites, females and adults.

Slide II shows that the patients who expired ranged from four months to 55 years but that no recoveries occurred in patients under ten months or over 35 years of age. Other factors influencing the recovery were freedom from miliary and other forms of tuberculosis. Thirty-three per cent of the expired cases had miliary tuberculosis in comparison with 13 per cent of the recovered cases. Seventeen per cent of the recovered cases had no other lesions as compared to six per cent of the expired cases. The duration of illness prior to the start of therapy was significantly different.

an average of 22 days had elapsed in the expired cases as compared to 13 days in the recovered cases and in nine selected cases in which therapy was instituted within 30 hours of the onset of symptoms there were no deaths

Slide III shows that there was no significant difference in the intramuscular streptomycin dosage between those which expired and those which recovered

Slide IV shows that 80 per cent of the patients treated with intramuscular streptomycin alone expired and 68 per cent of those who also received intrathecal streptomycin expired

Slide V shows that there was no significant difference in the intrathecal dosage between those who expired and those who recovered except that the same nine selected cases were treated for a period of 163 days instead of 80 days and consequently received a greater total amount of streptomycin. When these nine selected cases are removed from the recovered combined therapy group, the recovery rate of the remainder is no better than in the group treated with intramuscular therapy alone

With these statistics it would seem that we have a fairly strong case for early combined therapy and for prolonged treatment of both intramuscular and intrathecal varieties. Best results are obtained in the earlier treated cases and this is so important that I feel in doubtful cases one should err on the side of starting treatment early even at the expense of being required to explain a false start. This applies also to the use of intramuscular streptomycin in military tuberculosis. A small amount of streptomycin given while the diagnosis is being confirmed will probably do little or no harm and may mean the difference between success and failure of therapy.

How long does meningitis retain its responsiveness to streptomycin? At what stage of development is it no longer possible to get benefit from streptomycin? From our data it would seem that 21 days is beyond the point and 13 days is somewhere near the point of maximum duration of the disease when streptomycin may still be effective. Is it possible to enhance the effect of streptomycin with other drugs? We have no answers except that promizole and PAS are not tolerated well by children, that dihydrostreptomycin used in 12 meningitis cases produced startlingly bad results in all and that 10 meningitis cases now dead were treated with iodides without apparent benefit. Relapses will occur, however, I believe they will be less in evidence when prolonged treatment is used.

I compliment Dr. Shamaskin and his associates for their splendid work.

The Treatment of Tuberculous Tracheobronchitis with Streptomycin

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Introduction

Tuberculous tracheobronchitis is a frequent and important complication or concomitant finding in pulmonary tuberculosis. The stage, extent and course of the pathological bronchial changes usually determine the type of therapeutic procedures to be used for the control of the pulmonary tuberculosis. Treatment of tuberculous tracheobronchitis was unsatisfactory prior to the use of streptomycin. The prevention of chronic bronchial changes, such as tuberculous bronchiectasis and fibrostenosis, will solve many of the therapeutic problems of pulmonary tuberculosis. Successful control of the serious effects of tuberculous tracheobronchitis is essential to obtain satisfactory end results in the treatment of pulmonary tuberculosis.

Early reports by Brewer and Bogen,¹ and O'Keefe² indicated that ulcerogranulomatous lesions of the trachea and major bronchi responded well to combined intramuscular and inhalation treatment with streptomycin. Subsequently, inhalation therapy with streptomycin was found to be irritating and generally its use has been discarded. Pfuete and Pyle³ state, "Almost without exception, ulcerating and granulomatous lesions of the oropharynx, larynx and tracheobronchial tree have healed within a few weeks when streptomycin was administered." Tucker⁴ reports, "The effect of streptomycin on tuberculous lesions of the mucosa of the larynx and tracheobronchial tree is striking." The excellent cooperative study by the Veterans Administration, Army and Navy⁵ on the effects of streptomycin in the treatment of tuberculosis proves rather conclusively that this drug, in varying doses and regimens is capable of producing improvement in tuberculous tracheobronchitis and tuberculous laryngitis in 80 to 90 per cent of the cases selected for treatment.

Material

Clinical study of 25 patients with proved tuberculous bronchitis is the basis for this report. It is recognized that a presumptive diagnosis of tuberculous tracheobronchitis may be made on the

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basis of clinical and roentgenological findings but only those patients with demonstrable lesions in the major bronchi, as observed bronchoscopically, were included in this study

The pathological changes observed consisted primarily of ulcerations and granulations with associated hyperemia, edema and infiltration. Those patients who demonstrated only hyperemia, submucous tubercles or slight edema and infiltration were not considered as proved cases. Patients were also excluded if the bronchial tuberculosis had progressed to the stage of apparently healed fibrostenosis.

Bronchoscopic examinations were performed on all of the patients prior to the institution of treatment with streptomycin. Reexaminations were performed at intervals of two to four weeks during treatment and sufficiently often after therapy to determine the subsequent course. All of the bronchoscopic observations were made by the same bronchoscopist so that interpretation of the pathological changes and the results of treatment with streptomycin was uniform.

Treatment

We have been guided, in the main, by the recommendations of the Veterans Administration, Army and Navy in determining the regimens of treatment to be employed. Our earlier cases were given 0.2 gm. or 0.4 gm. of streptomycin by intramuscular injections five times daily for 60 to 120 days. It was soon noted that 1 gm. daily gave results comparable to 2 gm. and the frequency of administration was reduced to every 12 or 24 hours. The duration of treatment has varied from 30 to 120 days.

At the present time 1 gm. of streptomycin dissolved in 2 cc. of normal saline is given daily in a single intramuscular injection. Daily injections are continued for 30 to 90 days. The duration of treatment is determined by the rapidity of healing as observed by bronchoscopic examinations at two to four week intervals.

Plans for the permanent control of the pulmonary tuberculosis, whenever indicated, should be instituted prior to the use of streptomycin. Definitive treatment should be started as soon as feasible while the early beneficial effect of streptomycin is at its peak. Attack on the pulmonary tuberculosis at the earliest possible time is mandatory due to the emergence of resistant strains of tubercle bacilli as a result of treatment with streptomycin. Treatment should be continued only sufficiently long to obtain the desired effects in order to prevent or delay the development of resistant strains.

Results of Treatment

The 25 patients have been observed for a period ranging from

three to 27 months, with an average of 12 months, following completion of treatment with streptomycin. In 12 (48 per cent) of the patients, sputum or gastric cultures were converted from positive to negative. In four (16 per cent) patients, cultures which had converted to negative soon after treatment with streptomycin had been completed subsequently reverted to positive. Tubercle bacilli continued to be found in nine (36 per cent). Streptomycin should not receive the full credit for sputum or gastric conversion since some of the patients were treated subsequently with collapse or resection.

Tuberculous bronchitis was considered healed at the completion of treatment with streptomycin in 12 (48 per cent). In nine (36 per cent) patients the bronchitis was interpreted as showing marked improvement. In three patients slight improvement was noted and in one patient the bronchitis was considered unchanged. However, in two of the patients with slight improvement and in one patient with marked improvement, fibrostenosis subsequently developed.

Seven patients had some form of collapse therapy at the time the tuberculous bronchitis was recognized and in nine others collapse was instituted or resection performed following treatment. Sixteen (64 per cent) were thus aided by some type of collapse or resection in addition to streptomycin.

Comment

Streptomycin is an effective weapon against tuberculous tracheo-bronchitis. Definitive treatment may now be planned for many patients who formerly were doomed to develop irreversible chronic bronchial and pulmonary changes. Streptomycin must be fitted into a coordinated program of treatment and its use withheld until the optimal time.

The development of resistant strains of tubercle bacilli is the primary drawback to the use of streptomycin. This often precludes its use at a subsequent period when, at times, it may be needed urgently. Toxicity has been reduced to a minor problem since reduction of the standard dosage to 1 gm daily.

Symptomatic improvement may be dramatic when severe, intractable cough is present. Fever frequently is reduced to normal and there is improvement in appetite and gain in weight. Streptomycin exerts a tonic effect on the general condition.

Streptomycin is not recommended when tuberculous bronchitis has developed to the stage of healed fibrostenosis. Ulcers and ulcerogranulomas respond best and the visible lesions usually heal or show marked improvement within a few weeks. When the diagnosis of tuberculous tracheobronchitis or tuberculous bronchitis is based upon presumptive evidence alone, careful and continued

clinical observation should precede the use of streptomycin and its use should be part of a planned and coordinated attack upon the bronchial and pulmonary tuberculosis

SUMMARY

1) Streptomycin, in dosage of 1 gm daily, produced healing or marked improvement in 21 (84 per cent) of 25 patients with acute tuberculous bronchitis

2) The duration of treatment with streptomycin was determined by repeated bronchoscopic examinations and varied from 30 to 120 days in this series. At the present time treatment seldom exceeds 60 days

3) Measures to control the associated pulmonary tuberculosis should be instituted as soon as practical after therapy with streptomycin has been completed

4) Irreversible chronic bronchial and pulmonary changes may be averted by the judicious and timely use of streptomycin

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Topical Detergent Antibiotics in the Treatment of Tuberculous Sinuses

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Before the era of antibiotic therapy, one of the most difficult medical problems involved the treatment of chronic draining tuberculous sinuses. The advent of streptomycin and its use via the intramuscular route has brought definite clinical improvement, if not complete irradiation of the lesion, in a substantial proportion of treated patients.

In 12 cases reported by Brock¹ all but one of a total of 60 tuberculous sinuses were closed by intramuscular streptomycin administered over a period of one to 20 weeks. Streptomycin may, therefore, be regarded as by far the most effective agent for control of chronic tuberculous sinuses. At the same time close examination of the accepted method of administration suggests that certain improvements may be made in the technique of treatment.

Streptomycin therapy for tuberculous sinuses as practiced by Brock consists of the daily administration of 18 grams in six divided doses given intramuscularly. Six of his patients were treated for 90 days, and the remaining six for 150 days, with an untreated interval of three weeks following the first 90 days of streptomycin. Toxic reactions, including dizziness, headache and ataxia were observed.

The success of any plan of antibiotic therapy must depend on the production of a sustained inhibitory level of the drug at the site of infection. To this end, the treatment of an infected sinus tract by parenteral therapy represents, in our opinion, a relatively inefficient and wasteful procedure. A small fraction of the quantity of streptomycin required for intramuscular administration should produce a relatively enormous local concentration if introduced directly into the sinus tract where its ultimate activity must take place. The fact that an apparently great degree of efficiency is obtained in using antibiotics topically prompted the senior author to treat a woman suffering from a tuberculous sinus of seven years duration with streptomycin, using a surface active germicide as a solvent. Previous experience with antibiotics administered locally in solutions of reduced surface tension^{2, 4} indicated a logical extension to include infected sinus tracts of tuberculous origin.

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CASE HISTORY

The patient was a 36 year old white female who learned in August of 1934 that she had advanced pulmonary tuberculosis involving most of her left lung. In November of that year she was started on pneumothorax which was carried on until April of 1937 when she became febrile from infected pleural fluid. In smears and cultures the presence of *Mycobacterium tuberculosis* was established. Numerous forms of therapy, including thoracoplasty, were tried to control this unfortunate complication but all were unsatisfactory.

In January of 1939, a boggy inflammatory mass developed in the posterior aspect of the left axilla which spontaneously opened and discharged purulent material. Drainage persisted for seven years and nine months. Closure of the sinuses in October of 1946 was then accomplished by the use of topically applied streptomycin with a germicidal detergent.

Seventeen months later, after a severe nasopharyngitis, the patient noted a swelling over the lower portion of the previously closed sinus tract. She was immediately hospitalized after 15 ml of pus had been evacuated. Cultures, smears and biopsy of slough



FIGURE 1 The tuberculous sinuses noted above have been closed for over eighteen months following topical treatment with penicillin and streptomycin dissolved in a germicidal detergent solvent

that was removed failed to establish a diagnosis of tuberculosis. Nevertheless, on the basis of the past history, 4 ml of a solution of streptomycin and penicillin dissolved in a detergent solvent was instilled every eight hours night and day for 8 days and the sinus promptly closed. The solution was prepared by dissolving one million units of penicillin and one million units of streptomycin in 100 ml of zephiran chloride aqueous solution, 1:1000. In our original antibiotic detergent solution (October 13, 1946), we used only streptomycin, whereas in March, 1948 we combined streptomycin and penicillin with the germicidal detergent solvent. The chemicals are compatible and retain or exceed the component activity of streptomycin alone or penicillin alone when tested with *Staphylococcus aureus* or *Escherichia coli*.

The lesion treated by instillation of antibiotic detergent solution deep into the tuberculous sinus represents essentially a collapsed

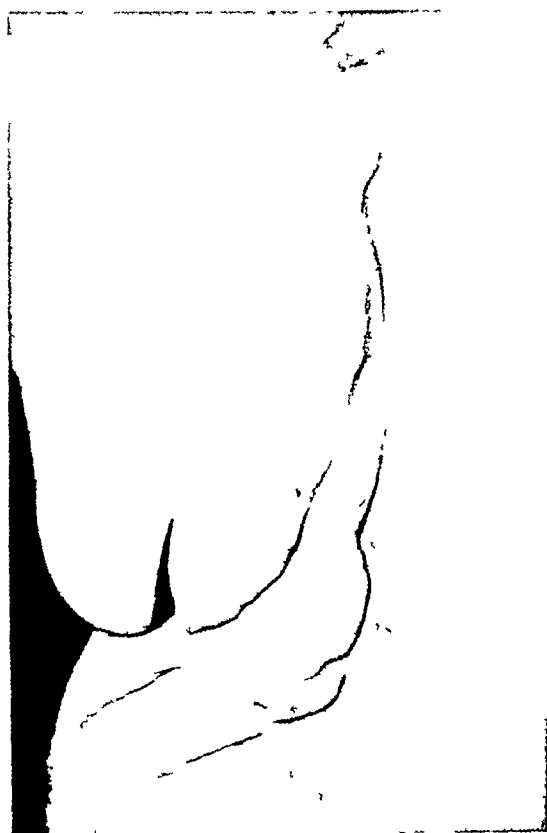


FIGURE 2 This picture shows all the sinuses closed after previously discharging purulent infected tuberculous material for over eight years. At various intervals there were six discharging sinuses and when treatment was started two were present.

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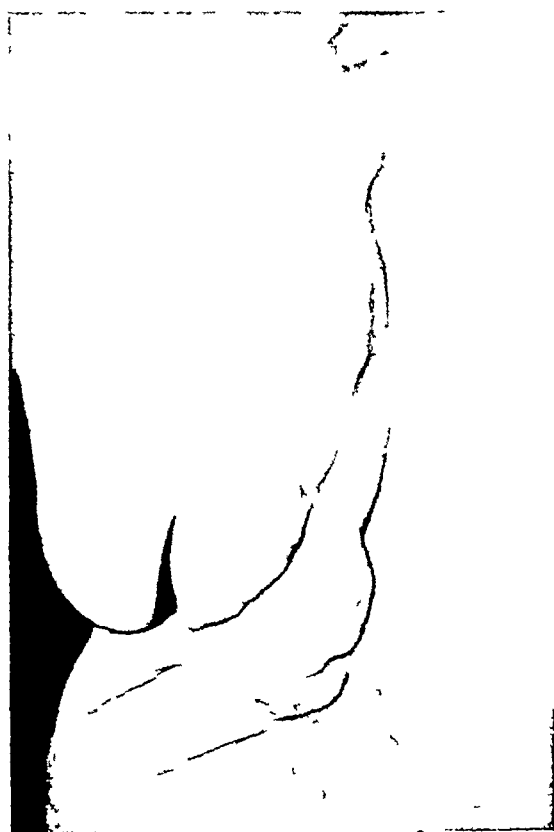


FIGURE 2 This picture shows all the sinuses closed after previously discharging purulent infected tuberculous material for over eight years. At various intervals there were six discharging sinuses and when treatment was started two were present.

chronic tuberculous empyema In the light of present trends to expand collapsed lungs by decortication, the original thoracoplasty may have been unwise A philosophy of conservative treatment is in keeping with the recommendation to use aerosolized detergent antibiotics by inhalation as the method of choice before resorting to collapse therapy

Previous experience in closing the draining sinuses of 35 patients suffering from chronic osteomyelitis prompted us to attack the more formidable problem of a known tuberculous sinus

The patient was emphatically instructed from the very outset to lie constantly on her right side so that the antibiotic detergent solution would drain by gravity into the ramifications of the sinus tract located on her left side, thereby attaining maximum topical efficiency Within four days the discharge from the sinus diminished markedly and the cavity closed completely at the end of 14 days Now, 15 months have elapsed and the sinuses are still closed with no evidence of any inflammatory reaction following this extraordinarily simple procedure

During the 14 years that this individual had been ill innumerable roentgenograms, blood studies, cultures, bacteriological

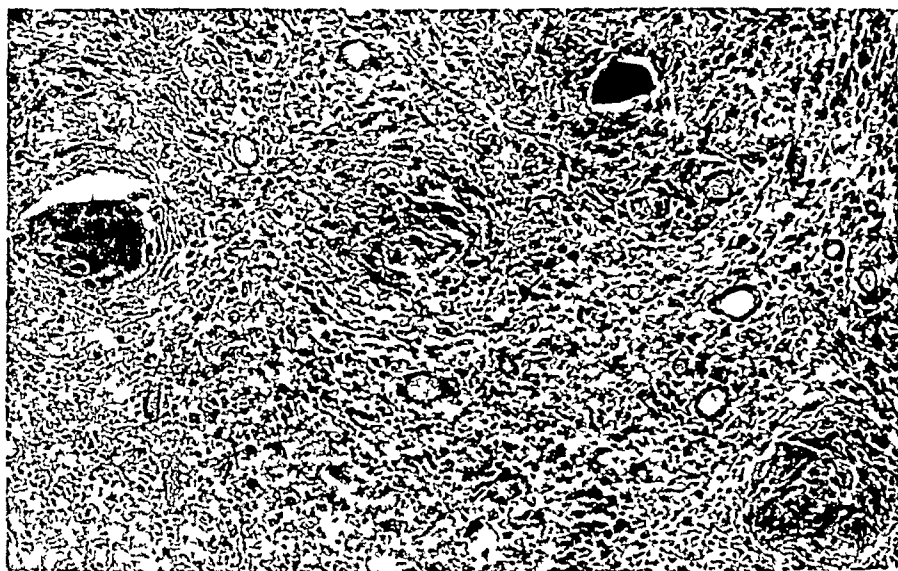


FIGURE 3 *Microscopic Examination* The particles are composed of compact fibrous tissue surmounted by stratified, squamous epithelium along one aspect They show focal hyperkeratosis, parakeratosis, vacuolization, atrophy and exfoliation in scattered areas Aggregations of polyblasts are evident in portions of the corium and are scattered through the foci of the subjacent dense fibrous connective tissue A few foci have circumscribed aggregations of epithelioid, lymphocytes, fibroblasts and multinucleated giant cells with central and peripheral distribution of nuclei The cells are grouped in fibrillar and fibrous reticulum showing granular fragmentation Rare acid fast rods are evident in some of the epithelioid cells after prolonged search

Diagnosis Chronic Inflammation, Focal Tuberculosis

studies, and other pertinent laboratory tests confirmed the clinical picture of a chronically ill patient suffering from tuberculous empyema with sinuses. A biopsy of the visceral and parietal pleura showed both grossly and microscopically the classical pathological picture of tuberculosis. In some fields it was possible, after prolonged search, to identify acid fast rods, probably *Mycobacterium tuberculosis*. Following the closure of these sinuses the entire clinical and laboratory picture promptly returned to one more normal.

Realizing the irreversible damage following thoracoplasty as practiced in the pre-antibiotic era, if confronted with this problem today, thoracoplasty would not be done so promptly. Using antibiotic detergent solutions topically in the empyemic cavity, we would try to expand the lung by decortication, and by aerosol therapy attempt to eliminate the primary source of disease in the lung parenchyma, in order to effect a cure.

X-ray inspection of the chest on January 28, 1948 revealed complete thoracoplasty on the left. No evidence of active disease was seen in the right lung. The mediastinal contents had shifted to the right. The vital capacity was 33 per cent of normal. Two recent vital capacity determinations were done on different days 15 months after closure of the sinus. In spite of diminished vital capacity the patient is able to carry on with her household duties. The alteration of her blood count from one indicative of pronounced anemia to normal may be another important factor in diminishing her dyspnea.

Discussion

Considerable theoretical evidence and some factual data are now available to indicate the importance of multiple chemotherapeutic agents in forestalling the development of resistant bacterial strains. No apparent antibacterial synergism is noted in zephiran streptomycin solutions, although this quarternary ammonium germicide has a powerful potentiating effect upon penicillin under certain conditions. The treatment of infected surfaces with solutions of reduced surface tension offers the advantage of enhanced penetration. However, quarternary ammonium compounds are considerably less effective in this respect than the esters of sodium sulfosuccinate we have employed previously in the treatment of osteomyelitis.

The clinician will be primarily interested in the rapid and successful closure of the sinus tract in this patient. As a comparison the report of Hinshaw et al.⁵ may be noted. Hinshaw, Feldman and Pfuetze, in reviewing 100 cases of tuberculous sinuses, report that, for satisfactory treatment, streptomycin therapy should not

be undertaken unless adequate amounts of the drug are available, that is, sufficient for a period of two to four months treatment, in which one to three grams is used daily for a total requirement of 360 grams

Advantages of the infinitely simple method of topical therapy become obvious when we consider the severe, often irreversible, toxic damage associated with prolonged use of streptomycin. In reviewing a series of cases given streptomycin parenterally over a long period of time, McDermott and his associates noted, with some concern, the systemic damage that might follow such a procedure. The simple topical approach, using streptomycin locally in a surface active germicide limits immediately the danger of systemic tissue damage because of the relatively minute amount used. With topical treatment there is virtual elimination of streptomycin penetrating into the systemic circulation for prolonged intervals of time, with the resulting possibility of tissue damage.

In contrast to the studies of Hinshaw and those of Brock, the method of treatment we suggest is distinguished by the rapidity of response and the brevity of the therapeutic program. In terms of conserved streptomycin, reduced hospitalization time and absence of prolonged dependence on our overstrained medical facilities the method deserves a thorough exploration by physicians dealing with the disabling lesion of chronic tuberculous sinus.

SUMMARY

In chronic infected sinuses, either tuberculous or non-tuberculous, the efficiency of the treatment will increase in direct proportion to the intimacy of the contact between the antibiotic and the pathogen. Using a quarternary ammonium compound (Zephiran) as a detergent with penicillin and streptomycin in very minute amounts, we have closed permanently a chronic tuberculous sinus. We emphasize the permanency of the closure because the technique described above, using known fundamentals in genetics, decreases the development of bacterial resistant strains. The simple topical approach, because of the relatively minute amount of streptomycin used, avoids the danger of systemic tissue damage.

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The Use of Dihydrostreptomycin in the Treatment of Tuberculosis*

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Although streptomycin is an invaluable drug in the treatment of certain types of tuberculosis, its neurotoxicity is a distinct disadvantage. This neurotoxicity, manifested by impaired function of the vestibular apparatus, almost always develops when a daily dose of 2 or 3 gm is given for a period of several weeks. The incidence is markedly decreased when the daily dose is reduced to 1 gm, but it is generally believed that this dose of the drug probably is inadequate for certain types of disease such as miliary and meningeal tuberculosis. Furthermore, convincing evidence has not yet been presented showing that a daily dose of 1 gm is as effective as twice this amount in the treatment of pulmonary tuberculosis and other less responsive types of the disease. The discovery of a new drug with the antituberculosis activity of streptomycin but with lessened neurotoxicity would be a distinct improvement, and preliminary studies suggest that dihydrostreptomycin has these characteristics.

Dihydrostreptomycin was first described in 1946 by Peck and co-workers.¹ Two other groups of workers^{2,3} independently reported the preparation of this same drug shortly thereafter. This new drug was prepared by the catalytic hydrogenation of streptomycin and was found to be more stable than the parent substance.

The effect of dihydrostreptomycin on tubercle bacilli was first studied by Youmans,⁴ who found that it had the same inhibitory effect as streptomycin on the growth of the H37Rv strain of tubercle bacilli in vitro. This has been confirmed by several groups⁵⁻⁹ working with numerous strains of tubercle bacilli with but one exception. Rake and his associates⁶ reported that they had found one strain of human tubercle bacilli for which the minimal inhibiting concentration of dihydrostreptomycin was consistently larger than that of streptomycin. The observation that streptomycin-resistant strains of tubercle bacilli are equally resistant to dihydrostreptomycin in vitro has been reported by several investigators.⁷⁻⁹

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The treatment of experimental tuberculosis in animals with dihydrostreptomycin was first reported by Freedlander and French,¹⁰ who found dihydrostreptomycin to have the same effect as streptomycin on experimental tuberculosis in guinea pigs. This has been confirmed by Feldman and his associates⁸ and these latter workers have shown that dihydrostreptomycin has no demonstrable effect on tuberculosis produced experimentally in guinea pigs by the injection of a streptomycin-resistant strain of tubercle bacilli. Rake and co-workers reported that the two drugs were equally effective against experimental tuberculosis in mice caused by the Ravenel strain of *Mycobacterium tuberculosis*, and Edison and her associates⁷ found the same to be true of avian tuberculosis in chicks.

The neurotoxicity of streptomycin and dihydrostreptomycin was compared in an experimental study by Edison and her associates using cats and dogs. They found that dihydrostreptomycin caused much less damage to the vestibular apparatus than did streptomycin. Similar findings in cats were reported by Hobson and his co-workers.⁹

The first clinical trials of dihydrostreptomycin were reported by Tompsett.¹¹ He gave the drug to five patients who had reacted unfavorably to streptomycin, four with drug fever and one with asthma. All five of these were able to take dihydrostreptomycin without difficulty.

After experimental studies in animals had shown that dihydrostreptomycin was as effective as streptomycin in controlling experimental tuberculosis and that it was less neurotoxic than streptomycin, a comprehensive study of the effects of dihydrostreptomycin on patients with tuberculosis was begun independently by two groups of investigators.^{9, 12} Both of these groups have made preliminary reports indicating that dihydrostreptomycin apparently has the same therapeutic effectiveness as streptomycin and that it causes much less damage to the vestibular apparatus. The concentration of dihydrostreptomycin in various body fluids has been studied by Hobson and his co-workers⁹ and by Levin and his co-workers,¹³ and the results of both of these investigators are comparable to the results in similar studies of streptomycin. Thus the apparent difference in the neurotoxicity of the two drugs could not be explained by differences in the concentrations of the drugs in the blood serum and other body fluids.

The present report is a summary of our experience with the first 35 patients whom we treated with dihydrostreptomycin.* Both

*The dihydrostreptomycin utilized in these studies was supplied by Merck & Co., Inc., Rahway, New Jersey, through Dr. James M. Carlisle and Dr. Augustus Gibson.

the hydrochloride and the sulfate forms of the drug were used, the concentration of each being 0.2 gm per cubic centimeter of distilled water. The drug was always given intramuscularly, the total daily dose usually being divided into injections of 1 gm at intervals of eight to 24 hours. The pertinent data regarding the occurrence of vestibular damage of these 35 patients are given in Table 1.

Neurotoxicity

Tests of vestibular function using the quantitative method of Kobrak were done on all patients before, during (usually at two-week intervals) and at the completion of treatment (except for one patient whose treatment was completed elsewhere). In addition, patients were questioned frequently regarding the occurrence of dizziness, deafness, visual disturbances and paresthesias. The infrequency of vestibular damage can be seen from the data in table 2.

Six patients have been given 3 gm of dihydrostreptomycin per day. One patient (case 1) received the drug for only 10 days and was comatose during this time owing to tuberculosis meningitis, so that tests of vestibular function could not be performed.

The patient in case 2 had first been treated with streptomycin, 2.8 gm per day for eight days, when symptoms of vestibular damage developed. Fourteen days later 2.0 gm of streptomycin per day was given for three days, and again administration of the drug had to be discontinued because of vertigo. After a lapse of six weeks she was given dihydrostreptomycin in a dose of 3.2 gm per day. After 20 days the dizziness returned and hypofunction of the labyrinths was noted. This patient had renal failure with a blood urea of 140 mg per 100 cc and the blood concentration of dihydrostreptomycin was found to be 320 micrograms per cubic centimeter of serum. The other four patients in this group received 3 gm of dihydrostreptomycin per day for 38 to 60 days. In case four mild vertigo developed after 42 days of treatment and the caloric test revealed slight bilateral hypofunction of the vestibular apparatus. Administration of the drug was stopped and the symptoms subsided within a week, and a caloric test eight months later revealed improvement in labyrinthine function in both sides, the left side being normal at this time. In the last of this group (case 6) no symptoms of vestibular damage developed and the results of the caloric tests performed every two weeks during treatment remained normal until the end of treatment, when slight bilateral hypofunction was noted.

Twenty-six patients have been treated with 2 gm of dihydrostreptomycin per day, most of them for 60 days. In only four of

TABLE 1
Data on 35 Patients Treated with Dihydrostreptomycin

Case	Age years and sex	Weight kg	DAILY DOSE		Injections per day	Days treated	Vestibular damage
			Gm	Mg /kg body weight			
1	39 M	?	3	?	3	10	?
2	49 F	83 2	3 2	38 5	8	20	Yes
3	56 M	?	3	?	3	38	No
4	32 M	93 2	3	32 2	3	42	Yes
5	56 F	52 7	3	56 9	3	60	No
6	30 F	47 3	3	63 4	3	60	Yes
7	52 M	90 5	2	22 1	1	42	No
8	24 F	50	2	40 0	2	9	
			2	40 0	1	36	
			1	20 0	1	15	Yes
9	44 F	58 6	2	34 1	1	49	
			1	17 1	1	11	Yes
10	33 F	42 7	2	46 8	1	60	Yes
11	46 M	78 2	2	25 6	1	60	No
12	66 F	39 5	2	50 6	2	35	No
13	33 F	55 0	2	36 4	2	44	
			1	18 2	1	7	Yes
14	21 F	49 1	1	20 4	1	22	
			2	40 7	2	42	No
15	49 M	57 3	2	34 9	2	60	No
16	30 F	73 2	2	27 3	2	60	No
17	43 M	58 2	2	34 4	2	60	No
18	33 M	77 3	2	25 9	2	60	No
19	39 M	72 7	2	27 5	2	60	No
20	30 F	55 0	2	36 4	2	60	No
21	40 F	60 0	2	33 3	2	60	No
22	56 F	55 5	2	36 0	2	60	No
23	40 M	74 5	2	26 8	2	60	No
24	75 M	51 4	2	38 9	2	60	No
25	42 M	75 5	2	26 5	2	60	No

TABLE 1 (Continued)

Case	Age years and sex	Weight kg	DAILY DOSE		Injections per day	Days treated	Vestibular damage
			Gm	Mg/kg body weight			
26	70 F	60.9	2	32.8	2	60	No
27	48 M	66.8	2	29.9	2	60	No
28	66 F	70.9	2	28.2	2	60	No
29	58 F	65.5	2	30.5	2	60	No
30	66 M	88.2	2	22.7	2	60	No
31	58 M	88.2	2	22.7	2	60	No
			2	22.7	1	90	
32	49 M	69.5	2	28.8	2	120	No
33	54 F	?	1	?	2	25	No
34	68 M	80.5	1	12.4	1	42	No
35	25 F	49.5	1	20.2	2	60	No
			1	20.2	1	60	

TABLE 2

Incidence of Vestibular Damage in Patients Treated
with Dihydrostreptomycin

Daily dose gm	Patients treated	Patients with vestibular damage
3	6	3
2	26	4
1	3	0

TABLE 3

Incidence of Vestibular Damage in Patients Treated with
2 Gm Dihydrostreptomycin per Day

Daily dose mg/kg body wt	Injections per day	Patients treated	Patients with vestibular damage
Less than 30.0	1	2	0
	2	10	0
More than 30.0	1	3	3
	2	11	1

these cases has any sign or symptom of neurotoxicity developed. The patient in case 13 received 2 gm a day in two injections for five weeks, after which right lower lobectomy was performed. The same regimen was continued postoperatively and on the forty-fourth day of treatment vertigo developed. The caloric test, which had previously been normal, then showed moderate hypofunction on the right side, the left remaining normal. The dose of dihydrostreptomycin was decreased to 1 gm per day in one injection but the symptoms persisted and another caloric test six days later revealed further impairment of the function of the right labyrinth. Administration of the drug was discontinued altogether, and a week later the vertigo had diminished appreciably although the results of the caloric test had not changed. This patient had a functionless kidney on the left side and the serum sulfate did increase to 6.5 mg per 100 cc about the time when the vertigo developed. However, the results of other tests of renal function, including the urea clearance test, were normal. The blood concentration of dihydrostreptomycin after the intramuscular injection of 1 gm of the drug was found to be 68.8 micrograms per cubic centimeter of serum after one hour and 14.9 micrograms after twelve and a half hours. Although these values are slightly higher than those reported by Levin and his co-workers after a similar injection, it is doubtful that the occurrence of vestibular damage in this patient can be attributed entirely to these concentrations of dihydrostreptomycin in the blood serum.

Another patient (case 8) was given a daily injection of 2 gm of dihydrostreptomycin for a tuberculous draining sinus of the left lumbar area. After 45 days of treatment she noticed slight vertigo and the caloric test revealed slight hypo-activity of the labyrinths on both sides. The dose of dihydrostreptomycin was decreased to 1 gm per day. By the end of the 60 days of treatment the vertigo was no longer present and a caloric test was reported to show bilateral normal labyrinthine function.

The patient in case 9 was also given a daily injection of 2 gm of dihydrostreptomycin. She also noted slight vertigo after 49 days of treatment. The caloric test, the results of which had been normal before and during treatment, then revealed a decrease in function of the right labyrinth, the left remaining normal. The dose of the drug was decreased to 1 gm per day and the vertigo diminished. However, the caloric test after a total of 60 days of treatment still revealed the same degree of decreased labyrinthine function on the right, the left side remaining unchanged.

The final patient to show any sign of vestibular damage (case 10) also received 2 gm per day in one injection. The caloric test that was done before the treatment was started revealed a slight bilateral

decrease in the function of the labyrinths. No symptoms of vestibular damage developed and caloric tests performed every other week showed no change until the final test, which was done after the sixty days of treatment had been completed. This showed a slight further bilateral decrease in the labyrinthine function.

The frequency of neurotoxic changes in the group which was treated with 2 gm of dihydrostreptomycin per day is summarized in table 3. Twelve of these patients received less than 30 mg per kilogram of body weight per day and in none of these cases did any vestibular damage develop. The remaining 14 were given more than 30 mg per kilogram of body weight per day. In 4 of these cases evidence of neurotoxicity developed. Three of the 14 patients received the total daily dose in one injection and all 3 of these sustained vestibular damage. In contrast, in only 1 patient of the 11 who got the same daily dose in two injections did such changes develop. Levin and his co-workers¹³ studied the concentration of dihydrostreptomycin in the blood serum of 3 patients who had received 2 gm of the drug in one injection and found it to vary from 119.2 to 214.4 micrograms per cubic centimeter one hour after the injection. Comparable concentrations of dihydrostreptomycin were probably present in the blood serum of this group of patients and it seems likely that the damage to the labyrinth was due to such high concentrations of the drug. For this reason we now believe that a daily dose of 2 gm should be divided into two injections at 12-hour intervals.

Three patients have been treated with a daily injection of 1 gm of dihydrostreptomycin without any sign or symptom of vestibular damage developing. The infrequency of neurotoxic reactions following the administration of dihydrostreptomycin is in marked contrast with our previous experience with streptomycin. A daily dose of 2 or 3 gm of streptomycin for several weeks was almost always followed by serious damage to the vestibular apparatus, and in nearly 50 per cent of the patients who were treated with only 1 gm per day some evidence of altered vestibular function developed. Although dihydrostreptomycin may cause similar changes, it does so infrequently and the damage is much less severe.

An occasional patient mentioned the occurrence of labial and digital tingling, but this usually subsided during treatment and was never of any serious consequence. One patient (case 10) noted that she was unable to hear her wrist watch tick for about six weeks after the completion of her treatment. However, when she was examined four months after the completion of the treatment she had no subjective deafness and an audiogram was normal. Another patient (case 15) complained of similar deafness and

an audiogram made four months after completion of his treatment revealed the development of deafness for the high tones (frequencies of 2,048 and higher) No other patient noticed any deafness and audiograms on 15 more of these patients from three to eight months after treatment did not reveal evidence of auditory damage

Allergic Manifestations

Allergic signs and symptoms were searched for and a weekly differential blood count was performed on most of the patients There were no allergic reactions, and one patient in whom a drug fever and an exfoliative dermatitis had developed from streptomycin was able to take dihydrostreptomycin without difficulty At the time of our preliminary report¹² we had not observed the development of eosinophilia, but we have subsequently detected 75 per cent or more of eosinophils (maximum 15.5 per cent) in nine patients However, there was no correlation between the size of the daily dose of dihydrostreptomycin and the occurrence of eosinophilia or between the eosinophilia and the manifestation of neurotoxicity

Systemic Toxicity

Twenty-one of these patients were studied intensively to detect any sign of damage to the kidneys or the liver, the function of these organs being tested at weekly to monthly intervals No evidence of damage to either system was detected Complete blood counts and a determination of the concentration of hemoglobin were done at weekly intervals and no sign of damage to the hematopoietic system was observed

In our previous report¹² we noted that two patients had complained of abdominal distress and gaseous dyspepsia which was relieved when the treatment was stopped We have not observed this in any additional cases

Local Irritation

We have studied the local irritation produced by numerous lots of dihydrostreptomycin, both in the form of the hydrochloride and of the sulfate Some of the early preparations caused a tender region of induration in the muscle at the site of the injection, but recently the preparations of dihydrostreptomycin have caused no more irritation than injections of similar amounts of streptomycin

The intrathecal injection of some of the early preparations of dihydrostreptomycin caused untoward reactions and led us to discontinue the administration of the drug by that route Al-

though we have not had occasion to resume the intrathecal administration of dihydrostreptomycin, we believe that the present preparations of dihydrostreptomycin would be satisfactory for intrathecal administration

Therapeutic Efficacy

Evidence has been presented showing that dihydrostreptomycin is as effective as streptomycin in inhibiting the growth of tubercle bacilli in vitro^{4,9} Likewise it has been shown that the two drugs are equally potent in suppressing experimental tuberculosis in chicks, mice and guinea pigs^{6,8,10} There has not yet been sufficient time to determine if dihydrostreptomycin is as effective as streptomycin in the treatment of various types of tuberculosis in humans, but it is our clinical impression that dihydrostreptomycin is the equal of streptomycin in this respect

Two of the patients in the present series were treated for nontuberculous conditions and two others have been under treatment for too short a period to determine whether or not there will be a satisfactory response Nine of these patients have far-advanced, fibrocavernous tuberculosis of the lungs which would not be expected to respond, and these patients were given dihydrostreptomycin along with promin and para-aminosalicylic acid to determine if the administration of other antituberculosis drugs along with dihydrostreptomycin would delay or prevent the emergence of dihydrostreptomycin-resistant strains of tubercle bacilli In five patients it was impossible to study the therapeutic efficacy of dihydrostreptomycin for various reasons, such as an inadequate period of treatment or the surgical removal of the diseased portion of lung This leaves 17 patients in whose cases the therapeutic effect of the drug could be evaluated, and we feel that these patients responded to treatment just as we would have expected them to do if they had been given streptomycin instead of dihydrostreptomycin

The following cases are examples of responses which we have seen

Tuberculous Sinuses

The patient in case 10 first came to the Mayo Clinic in 1918 at the age of 3 years, at which time she was found to have tuberculosis of the lumbar vertebrae A draining sinus developed in the right groin in 1920 at the age of five years, and subsequently others developed in the left groin and one in each lumbar region She was treated with rest and suitable braces and corsets with satisfactory control of the vertebral disease Some of the sinuses ceased to drain for short periods but at least one of them was discharging pus at all times from 1920 until we saw her in November 1948 At that time the one in the left lumbar region had drained con-

tinuously for 20 years and the ones in the left groin had been open for 17 years (Fig 1a) Treatment with dihydrostreptomycin was advised and she was given 2 gm of the drug (46.8 mg per kilogram of body weight) intramuscularly each morning for 60 days She was also given 15 gm of para-aminosalicylic acid* orally three times daily and 0.4 gm of promin* once each day in an effort to delay or prevent the emergence of dihydrostreptomycin-resistant strains of tubercle bacilli¹⁴

The response to this regimen of treatment was remarkable All four of the sinuses had ceased to drain by the 18th day of treatment, and for the first time in 28 years she did not have to wear a dressing to absorb the pus The healing continued and the openings of the sinuses were well epithelized by the 60th day (Fig 1b) She was re-examined four months later and found to be well with the sinuses still closed

Comment — Four other patients with tuberculous sinuses of the neck, thoracic wall, lumbar region and groin responded to treatment with dihydrostreptomycin in an equally gratifying way These results were the equal of any that we have seen from the use of streptomycin

Tuberculosis of the Lungs

The patient in case 6, a Negro woman aged 30 years, registered at the clinic on September 22, 1948 She complained of hoarseness of 10 months' duration Examination of the larynx revealed an extensive ulcerating lesion characteristic of tuberculosis Although the patient had no other symptoms, a roentgenogram of the thorax revealed caseocavernous lesions of both lungs (Fig 2a) and those of the thoracic segment of the

*The para-aminosalicylic acid and promin utilized in these studies were supplied by Parke, Davis & Company, Detroit, Michigan, through Dr E A Sharp

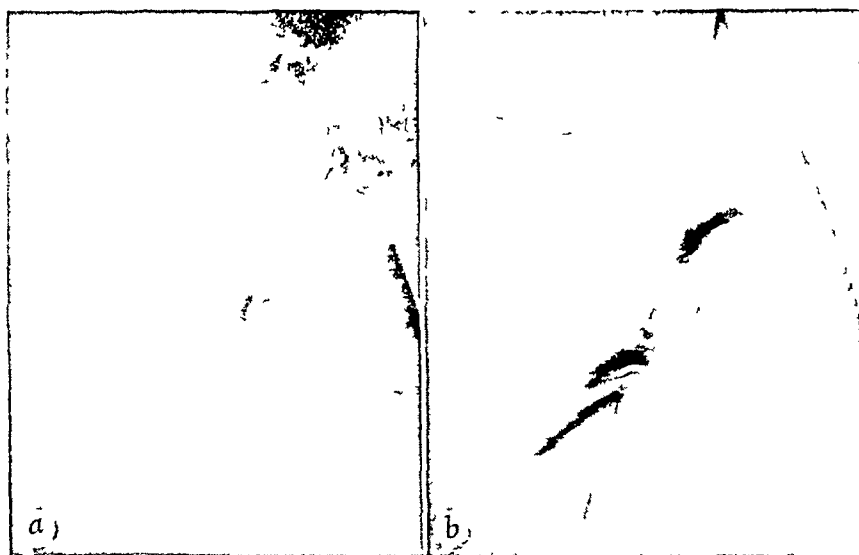


FIGURE 1 Draining sinuses in groin of patient in case 10, (a) before, and (b) after treatment

spinal column revealed tuberculosis of the eleventh and twelfth thoracic vertebrae. A stained smear of the sputum was positive for acid-fast bacilli. She was hospitalized at once for strict rest in bed and was given 1 gm of dihydrostreptomycin intramuscularly every eight hours (63.4 mg per kilogram of body weight per day). A re-examination of the larynx after four weeks of treatment showed marked improvement, and after 60 days of treatment the larynx appeared to be normal except for slight thickening of the vocal cords. Serial roentgenograms of the thorax showed progressive improvement of the pulmonary lesions (Fig. 2b), and the sputum became negative for acid-fast bacilli by the concentration method. However, cultures of the sputum were still positive for acid-fast organisms. There was no demonstrable change in the appearance of the vertebral lesion during the 60 days of treatment. After this period of treatment with dihydrostreptomycin the patient transferred to a tuberculosis sanatorium in her home state for completion of her treatment.

The patient in case 11, a white man aged 43 years, was found to have active tuberculosis of the lungs with nodular and fibrotic lesions throughout both lungs in September, 1945. A stained smear of the sputum was positive for acid-fast bacilli. He entered a tuberculosis hospital where he remained for two years, during which time he was treated with rest in bed, right phrenemphraxis and pneumoperitoneum. His lesions became stable by serial roentgenograms and the sputum became negative for acid-fast bacilli. However, the cultures of the gastric washings remained positive for acid-fast bacilli. He was dismissed from the sanatorium in November, 1947, to continue rest and pneumoperitoneum therapy under



FIGURE 2a. Roentgenogram of left upper lung field of patient in case 6 showing large cavity present before treatment. (b) Same area after treatment.

pariente, tanto in vitro como en la tuberculosis experimental en diversos animales. La neurotoxicidad de las dos drogas se ha estudiado también experimentalmente y la dihidroestreptomycinina se ha encontrado menos tóxica.

La presente comunicación resume nuestra experiencia con los primeros 35 enfermos tratados con la nueva droga. La dihidroestreptomycinina se ha encontrado menos neurotóxica que la estreptomycinina, solo 4 de 26 enfermos mostraron algún signo de daño vestibular cuando se dió una dosis diaria de 2 gms por largos periodos. Dos enfermos notaron ligera sordera después de terminado el tratamiento y los audiogramas demostraron el desarrollo de sordera para las altas frecuencias en uno de ellos.

No ocurrieron reacciones alérgicas aunque 9 de 35 enfermos tuvieron 75 por ciento o más de eosinófilos. No se encontraron otros cambios en la sangre. El estudio de las funciones hepática y renal no reveló daño alguno a estos órganos. La dihidroestreptomycinina pareció tan efectiva como la estreptomycinina en el tratamiento de varias formas de tuberculosis, pero se requiere mucho trabajo en adelante para determinar si las mismas dosis de las dos drogas son igualmente efectivas. La frecuencia de las cepas dihidroestreptomycinino-resistentes no es aun conocida, pero tres de los enfermos eliminaron bacilos resistentes durante el tratamiento, uno de ellos apenas después de 18 días de tratamiento.

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D I S C U S S I O N

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In discussing Dr Carr's paper I shall limit myself to the clinical aspects of the "Case of Dihydrostreptomycin," since this new drug has not been the answer to the drug resistance bug-a-boo which has so handicapped us with the older drug streptomycin. As Dr Carr has pointed out, resistance to the one connotes resistance to the other.

In many respects I am in complete agreement with the Mayo group's conclusions concerning the toxicity of dihydrostreptomycin but there are one or two differences in our thoughts which concerns first the neurotoxicity, and second the therapeutic efficacy of the drug.

You have learned from Dr Carr's paper that 35 patients were treated with 1 to 3 grams of the drug daily for periods ranging from eight to 150 days. In analyzing these treatment periods it will be seen that one patient was treated 150 days, one 120 days, one 64 days, 24 60 days, one 51 days, and seven 42 days or less. In other words 32 patients of the group of 35 were treated for 60 days or less. I believe that this fact accounts entirely for the discrepancies in neurotoxic manifestations in the Mayo group and in our group treated at Rutland Heights. We treated 20 patients with daily dosage of 2 to 3 grams, 2 grams in 10 cases and 3 in 10, for a period of 90 days with one exception, the case of a man of 24 years of age who had vestibular loss on the 60th day of treatment (daily dose of 3 grams) at which time the drug was discontinued.

Reviewing the toxic manifestations we have observed we are in agreement with the observations made by Dr Carr and his co-workers except as regards neurotoxicity and more specifically as regards involvement of the cochlear nerve.

We have observed no allergic skin reactions either in the patients being treated or in the nurses giving the injections. Rashes, so common in streptomycin treated cases, were not observed. There were no cases of drug fever. We had six patients (30 per cent)

who showed an eosinophilia which ranged between 5 and 8 per cent This is a little above the upper limit of normal and in sharp contrast to the eosinophilias of 15 and 20 per cent so commonly observed in the streptomycin treated cases

Except for an early drop in red counts in nine patients (45 per cent) which soon returned to normal in spite of continued treatment and which is probably without much significance, there was no apparent damage to the hematopoietic system

There was no conclusive evidence of renal or liver damage, the function of these organs being tested at various intervals Two patients had slight nausea early in treatment which was not very impressive and no dose of the drug was omitted because of it

Concerning local irritability of the drug, all patients complained of burning pain immediately after injections and soreness at the site of injections when the early lots of the drug were used At that time we were using the dihydrostreptomycin hydrochloride "Merck" This was much more marked than in the case of streptomycin With subsequent lots which presumably were more purified, however, we had less complaints from the patients who at first were almost on the verge of mutiny I believe that I was the first to use the new sulfate which Dr Carlisle of the Merck Company sent me to try on our group Testing the entire group of 20 patients with injections of the sulfate in their left arms and an equal amount of the hydrochloride in their right 19 patients complained of pain in their right or hydrochloride arm and none in their left or sulfate arm, the exception being a man in complete euphoria who had no pain in either

Concerning vestibular damage we had only one patient who demonstrated any substantial degree of vestibular involvement as determined by the Kobrak test I mentioned him before

Four patients of our group (20 per cent) developed definite evidence of cochlear nerve involvement which was revealed both clinically and audiometrically Strange to say these changes did not appear until after completion of the 90 days course, with one exception, the man who lost vestibular function He developed some tinnitus toward the end of his second month of treatment and an audiogram taken on his 60th day revealed some loss in the high tones Subsequent audiograms in this patient revealed further hearing loss and his tinnitus continued for a few weeks but now, six months later it has disappeared He has no dizziness or ataxia of any degree now but his vestibular function has not returned

The second patient who showed some cochlear nerve involvement, the only one who was receiving 2 grams daily in the group of four who showed evidences of neurotoxicity, was a 52 year old

white male who complained of tinnitus one month after completing his 90 day course. An audiogram at this time revealed some loss in the higher tones. His tinnitus has persisted to the present, three months post-treatment. He has no clinical deafness. Concomitantly with his tinnitus he complained of occasional staggering, especially in the dark, and loss of balance when bending over. The Kobrak test did not reveal vestibular loss.

The third patient, a man of 30, revealed no evidence of cochlear nerve involvement until two months post-treatment when he developed tinnitus and some deafness. His audiogram for the first time revealed some loss of function.

The fourth patient, a man 37 years of age had no symptoms until one month following the completion of his 90 day course. At this time he had tinnitus and mild deafness, both of which increased markedly in severity up to the present. Audiograms taken at the onset of tinnitus revealed hearing loss and subsequent audiograms have been worse.

In addition to these four patients in our group of 20, who developed cochlear nerve involvement, I wish to mention another, that of a negro in his early twenties who was admitted to Rutland with acute generalized milary tuberculosis without evidence of meningitis. He had been given two months of dihydrostreptomycin in a dosage of 3 grams daily at another hospital prior to admission. Because of our milary protocol we switched to streptomycin in a dosage of 2 grams daily. At the end of one month of such treatment he complained of tinnitus and deafness and an audiogram revealed considerable loss of function. His deafness rapidly became worse until he was completely deaf. Since in treating well over 300 cases with streptomycin in dosage from 1 to 3 grams daily for periods ranging from 42 to 150 days, we had no evidence of deafness and no audiometric changes of any degree, we believe that this patient's deafness was due to the two months of dihydrostreptomycin he received before he came to us rather than to the streptomycin he received from us for a month.

The fact that we are observing cochlear nerve involvement in dihydrostreptomycin treated cases alters our earlier impression that this drug was relatively non-toxic.

I cannot entirely subscribe to Dr. Carr's impression that therapeutically dihydrostreptomycin is as effective gram for gram as streptomycin. In reviewing our roentgenograms we concluded that only 65 per cent had shown improvement and then the improvement was mostly slight or at most moderate. This is at variance with our streptomycin groups who demonstrated improvement between 80 and 90 per cent and then at times to marked degree. However, in such a small series it would be foolish to base too

much on these figures. Hundreds of cases must be studied before any true conclusions concerning the superiority of one of these drugs over the other can be determined.

In conclusion, then, it would seem that in most respects dihydrostreptomycin was less toxic than streptomycin but in regard to neurotoxicity directed against the cochlear nerve the reverse is true. It seems quite probable that we have delayed vestibular damage by the hydrogenation of streptomycin to form dihydrostreptomycin but at the expense of hastening or increasing damage to the cochlear nerve.

Except for further careful study with dihydrostreptomycin, which should be carried out, I should recommend the drug therapeutically only in those cases who have demonstrated sensitivity to streptomycin and then only in a dosage below 2 grams and for periods of 60 days or less.

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Dr. Carr has presented in clear and concise form information that will be valuable to all who are treating tuberculosis. There have been and are many methods of administering streptomycin as to dosage and time interval between doses, but it is apparent that the large doses given in the earlier use of this drug are definitely tapering off. Invariably when large doses of streptomycin sulfate were used, vestibular damage began to show up anywhere from one week on, and in many cases, it was necessary to discontinue the treatment due to increasing symptomatology affecting the vestibular system.

At that time we were not doing sensitivity tests with streptomycin and no doubt resistant strains of tubercle bacilli often developed, making useless any further treatment at that time. However, we were proceeding on the empirical formula of giving it from three to four months in large doses.

One case of tuberculous meningitis was treated with streptomycin sulfate in the dosage of 3 gm daily and 200 mg daily intrathecally for 123 days. At the end of 10 weeks of streptomycin sulfate therapy, there was little if any improvement. Tubercle bacilli were still present in the spinal fluid and it was then that streptomycin dihydrochloride became available and we changed to that form. Immediate improvement was noted, and at the end of 123 consecutive days of streptomycin, treatment was discontinued as her temperature and spinal fluid were normal and she was developing some local reaction from the intrathecal injection.

tions After two years, the patient is alive and well although she is totally deaf, and this damage started early in the treatment of the tuberculous meningitis. However, we decided that it was better to have a deaf person and living, so we continued treatment irrespective of the vestibular damage. She was also extremely dizzy during treatment. Apparently this person did not develop a resistant strain of tubercle bacilli as improvement started 10 weeks after treatment was started.

Another patient treated for three months following the removal of a tuberculous kidney received 1.5 gm daily for 85 days and was not tested for resistant strains of tubercle bacilli. The only reaction he developed was disturbance of equilibrium which persists one year later. His hearing is not at all diminished but his equilibrium does not function when he leans forward as he is liable to keep on falling.

Pulmonary cases treated with streptomycin in the 3 gm dosage invariably developed symptoms affecting the vestibular system and also various other manifestations such as skin and gastrointestinal reactions. In these cases where vestibular damage or any other reaction was beginning to show, symptomatology, streptomycin was discontinued and in most cases, with the exception of the two above noted, the damage disappeared to a great extent.

When dihydrostreptomycin became available, it was used in the dosage of 1 to 1.5 gm daily in two equally divided doses and 39 cases have been treated and are under treatment with this preparation. One case in particular who could not take streptomycin sulfate without developing a severe allergic reaction in the form of an intense irritation of the skin and a severe swelling of the face, was started on dihydrostreptomycin in the dosage of 0.1 gm daily for one week to determine if dihydrostreptomycin could be taken without reaction. No reaction occurring, the dosage was increased to 1 gm daily and no reaction developed. This has been the experience of many in our cases.

Two cases, one bilateral far advanced, exudative in type, and one with a bronchopneumonic spread to the contralateral lung showed dramatic improvement in one month and the sputum converted in the first case in four weeks and in the second case in six weeks.

After our initial period of using large doses of streptomycin sulfate and the dihydrostreptomycin and the calcium chloride complex, we decreased the dosage of these preparations to 1.5 gm or 1 gm and the reactions were less in number and less severe, and in practically all cases when the drug was withdrawn the damage disappeared to a great extent.

In November 1948, we started using dihydrostreptomycin in the

dosage of 1 to 1.5 gm (mostly 1 gm) in two equally divided doses and in no case have we given over 1.5 gm. Following this regime, all the reactions noted were slight dizziness in two cases and impaired hearing in one. These symptoms disappeared when the dihydrostreptomycin was discontinued. Therefore as dihydrostreptomycin was not given in large dosage, we have no way of comparing the reactions which might have occurred with dihydrostreptomycin in the same dosage as streptomycin sulfate.

When dihydrostreptomycin was started, we also began making sensitivity tests so as to ascertain if resistant strains of tubercle bacilli were developing and in about 40 per cent of the 39 cases, treatment was discontinued as a resistant strain was developing to such an extent that the drug was not of further use, and some cases were discontinued as treatment did not seem to be of value. In our experience when a resistant strain of tubercle bacilli developed early in the treatment, it increased rapidly, and after two or three months of no therapy the resistant strain remained and we could not again use dihydrostreptomycin.

As to local reactions, dihydrostreptomycin did not cause so many or so severe ones as streptomycin.

In laryngeal tuberculosis we have obtained excellent results insofar as the laryngitis is concerned with the dosage of 0.2 gm daily. Many of these cases were far advanced terminal cases and it was given with the one idea of making the patient comfortable and able to eat. Without exception we were able to accomplish this in these cases. One case before admittance had a biopsy taken from the epiglottis leaving a large punched out hole with severe swelling of the surrounding tissues. Dihydrostreptomycin was immediately started in 1 gm dosage and the surrounding edema and infiltration subsided rapidly and she was able to swallow and the pulmonary tuberculosis soon became inactive.

In the treatment of tuberculous sinuses, we have had excellent results in two cases. Both of them were of long standing but they immediately began to improve under treatment with dihydrostreptomycin. In the treatment of pulmonary tuberculosis, our cases were not too carefully selected and our results consequently were not of the best.

In resistant cases, we are now starting to use PAS but it has not been employed for a sufficient length of time to determine if it will reduce the resistant strain of tubercle bacilli or whether it will be efficacious if given alone. However, we are becoming more cautious in the use of dihydrostreptomycin and in many cases are reserving it for an emergency or when we think surgery will be necessary. We have started using dihydrostreptomycin in 2 gm doses given at one time every two days.

I am in agreement with Dr Carr that dihydrostreptomycin should not be used in the treatment of pulmonary tuberculosis when we think there is a reasonable chance for the disease to become arrested with bed rest and collapse therapy, and I do not think that the drug should be used indiscriminately in all cases of tuberculosis

Antibiotics in Non-Tuberculous Pulmonary Diseases*

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The introduction of antibiotics has revolutionized the treatment of pulmonary disease. With the rapid discovery of new antibiotics, an increasing number of inflammatory lung lesions is rapidly being brought under control. It is proposed in this paper to describe the practical use of the antibiotics in non-tuberculous diseases of the chest. The useful antibiotics will be discussed in detail and some of the newer ones mentioned. The treatment of the following pulmonary diseases will be considered: Pneumonia, lung abscess, bronchitis, bronchiectasis and empyema.

Up to the present time over 100 antibiotics have been isolated, but only a few of these have practical value in the treatment of pulmonary disease. Many others will unquestionably be added as refinements in preparation and means of overcoming toxicity are discovered. At this writing, four of the antibiotics are available for treatment of pulmonary diseases, penicillin, streptomycin, aureomycin and chloromycetin.

1 *Antibiotics Useful in Pulmonary Diseases*

Penicillin Penicillin is derived from the common mold, *Penicillin notatum*. It was first discovered by Fleming^{1,2} in 1928. The most widely used preparation is crystalline penicillin G, readily soluble in water. It is the drug of choice in pulmonary infections caused by the following organisms: 1) *Diplococcus Pneumoniae*, 2) *Streptococcus*, 3) *Staphylococcus*, 4) *Actinomyces Bovis*, and 5) *Spirochaetes*.

The drug is non-toxic except for the occasional allergic reactions of dermatitis, urticaria and fever which can be readily controlled with anti-histaminics or by changing the brand of penicillin. Resistance rarely develops following penicillin therapy.

The best method of administration is by the intramuscular route, using 50,000 units of the sodium or potassium salt of penicillin G in aqueous solution every three hours around the clock. This produces quick and adequate plasma concentrations of penicillin. The dosage may be increased to 100,000 units or decreased to 25,000 units depending on the severity or mildness of the infection. Pro-

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came penicillin G is a salt that is relatively insoluble in water and releases penicillin slowly following an intramuscular injection. A single injection of 300,000 units of procaine penicillin gives an adequate blood level for at least 12 to 24 hours, so that two such injections 12 hours apart would be adequate for most infections. The addition of 100,000 units of sodium or potassium penicillin G to the procaine penicillin provides both rapid and prolonged action up to 24 hours. When repeated injections of crystalline penicillin are not feasible, as in home therapy, the longer acting procaine penicillin should be used. Oral penicillin of the sodium or potassium salt of crystalline penicillin may be used when the parenteral method is impossible. However, five times the estimated parenteral dose must be prescribed. While the oral method has received adequate trial with considerable success, it should never be the route of choice in a severe infection.

The inhalation of vaporized solutions of penicillin is of considerable value in the treatment of broncho-pulmonary disease. From 25,000 to 50,000 units of penicillin dissolved in 1 cc of physiological saline solution are inhaled three to five times daily by means of a vaponefrin nebulizer, preferably attached to an oxygen tank by rubber tubing. Green³ suggests the use of Laboratory aerosol in the dilutions, and at times epinephrine and pyribenzamine solution. He states that with these solutions, local reactions to penicillin in the nose and throat are eradicated.

Intratracheal solutions of penicillin may be used and have been found to be of value where the drug is indicated. For this, 50,000 units are dissolved in 3 cc of physiological saline and introduced with a catheter. Penicillin may also be combined with lipiodol, 1,500 units to 1 cc of oil, and introduced as in ordinary bronchography.

Streptomycin. Streptomycin was first described by Schatz, Bugie and Waksman⁴ in 1944. It is derived from certain strains of *Actinomyces griseus*. It is prepared in powder form, readily soluble in water or saline. The chief value of streptomycin lies in its potency against many gram-negative organisms resistant to penicillin. It is the drug of choice in the following infections involving the lungs, either primarily or secondarily: 1) *Klebsiella pneumoniae* (Friedlander's bacillus), 2) *Pasteurella tularensis*, 3) *Pasteurella pestis*, 4) *Haemophilus influenzae*, 5) *E. Coli*, 6) *Bacillus Pyocyaneus*, 7) *Brucella* species (with sulfonamides).

Streptomycin is more toxic than penicillin particularly if given over a long period of time. Allergic reactions such as fever and urticaria are usually not severe and can be controlled with antihistaminics. When the drug is given in large doses longer than three weeks, involvement of the eighth nerve may take place caus-

ing vertigo, tinnitus and deafness. Even the severe cases of vertigo however, eventually compensate in spite of irreparable damage to the vestibular system. Resistance develops in the majority of cases if the drug is used a long time, starting approximately five weeks after beginning of streptomycin therapy.

The best method of administration is the intermittent intramuscular one. For the average infection, 0.5 gram every 6 hours around the clock is sufficient. As much as 4 grams daily may be necessary in severe infections.

Aerosol streptomycin is of value in infections due to gram-negative organisms. The method is the same one described in aerosol penicillin therapy, using 50,000 units of the drug dissolved in 1 cc of physiological saline solution and repeated three to five times daily. Direct instillation into the trachea may also be used as described above.

Aureomycin Aureomycin was isolated by Duggar⁵ in 1948 from *Streptomyces aureofaciens*. It is a yellow crystalline powder, soluble in water and contains nonionic chlorine. It is the drug of choice in the following pulmonary infections: 1) Primary atypical (viral) pneumonia, 2) Ornithosis and Psittacosis, 3) Rickettsiae Species, 4) Salmonellae Species, 5) Bacterial pneumonia (pneumococcal, streptococcal, staphylococcal and hemophilus influenza infections, particularly if penicillin and streptomycin have failed), 6) *Pasteurella Tularensis*, 7) *Brucella* Species, 8) *Endameba Histolytica*.

Aureomycin is non-toxic, the only disturbing effects being occasional nausea, vomiting and diarrhea. Aluminum hydroxide offsets the nausea. The reactions may be due to impurities in the drug and do not usually necessitate discontinuing treatment. Development of resistance rarely occurs with aureomycin.

Oral dosage is the best method of administration. One gram every four to six hours for several days or until improvement occurs followed by 0.5 gram every six hours is the optimum dosage. Intramuscular therapy is usually accompanied by pain and induration at the site of injection. Intravenous therapy given in 1 per cent solution slowly may be used.

Chloromycetin Chloromycetin was isolated by Ehrlich and Burkholder⁶ from *Streptomyces venezuelae* in 1947 and can also be prepared synthetically. This compound contains nonionic chlorine. It is the drug of choice in the following infections which may primarily or secondarily involve the lungs: 1) Rickettsial species (especially typhus fever), 2) Ornithosis and Psittacosis, 3) *Salmonella* species (may be better than aureomycin), 4) Atypical pneumonia, 5) *E. Coli* infections, 6) *Brucella* species.

Chloromycetin is relatively non-toxic. It is given by mouth, starting with 1 gram dosage every four hours until clinical im-

provement occurs and later 0.5 gram every six hours. Treatment should be continued for three to five days following drop in fever.

It is noted that both aureomycin and chloromycetin have similar therapeutic effectiveness. It would appear at this time however, that aureomycin should be preferred for atypical pneumonia, the ornithosis-psitticosis group, tularemic pneumonia, Rocky Mountain spotted fever and Q fever infections. Chloromycetin appears to be more effective for typhoid, typhus and the salmonella group of infections. Both are apparently effective in brucellosis.

Some of the more promising antibiotics not yet ready for general use should be mentioned at this time.

Polymixin Polymixin is derived from soil organism B. Polymixa. It is the most effective drug for gram-negative bacilli but is toxic to the kidney. It is more active than streptomycin against streptomycin sensitive gram-negative organisms, and is also active against streptomycin-resistant gram-negative organisms.⁷

Subtilin Subtilin is produced by a strain of B. Subtilis. It is active against gram-positive bacteria, M. Tuberculosis, some of the fungi and E. Histolytica. It has a very low toxicity.

Bacitracin Bacitracin is derived from strains of B. Subtilis. It is very active against gram-positive bacteria, and has been widely used in surgical infections. Its nephrotoxicity makes it unsuitable for systemic use.

Streptothricin Streptothricin is derived from strains of Streptomyces lavendulae. It is active against fungi, but is toxic to animals.

Actidione Actidione is produced by strains of Streptomyces griseus. It is active against yeasts and fungi, particularly Torula, but has received only limited clinical trial.

Neomycin Neomycin is derived from Streptomyces fradiae. It is active against mycobacteria and streptomycin-resistant organisms. Its clinical value has not yet been established.

2 Pulmonary Diseases Favorably Influenced by Antibiotic Therapy

The most important application of the antibiotic therapy in pulmonary disease is in the treatment of pneumonia. There is now at hand a specific antibiotic for every form of pneumonia except that type due to the smaller viruses. The drug of choice and dosage is given in the following paragraphs.

Pneumococcal Pneumonia Penicillin is so highly specific against the pneumococcus, that it is the drug of choice in the treatment of pneumococcal pneumonia. The sulfonamides are relegated to second choice because of their potential toxicity and somewhat lesser potency. Penicillin is best administered by three

hourly intramuscular injections of 50,000 units of crystalline penicillin Therapy should be maintained for five to seven days after the crisis Intramuscular administration of 300,000 units of aqueous penicillin or procaine penicillin G at 12 hour intervals give just as good results It is likely that much smaller doses would be adequate in the average case of pneumonia, but it would be unwise to chance inadequate therapy

Streptococcal Pneumonia Penicillin is highly effective in the treatment of streptococcal pneumonia Treatment should be intensive and the doses of penicillin high

Staphylococcal Pneumonia Penicillin is the drug of choice in staphylococcal pneumonia Large doses should be used Aureomycin may be of value in those cases in which the organisms have been found to be penicillin-resistant Children with staphylococcal infections associated with pancreatic fibrosis who did not respond to penicillin were markedly benefited by aureomycin⁹

Friedlander's Pneumonia Friedlander's bacillus is sensitive to streptomycin and should be used in all cases The dose should be large at the onset, usually 4 gms daily, 1 gm given intramuscularly at six hour intervals The dose should be cut down to 2 gms daily as soon as a therapeutic effect is obtained

Hemophilus Influenzae Pneumonia Pneumonia due to hemophilus influenzae responds promptly to streptomycin Two to 4 gms of the drug are given daily for approximately 10 days Aureomycin has been found to be effective in infections due to hemophilus influenzae and should be used if streptomycin fails

Viral Pneumonia The pneumonias due to filtrable viruses may be classified into primary atypical pneumonias of unknown etiology and viral pneumonias of known etiology In the latter group are included 1) Influenzal pneumonia, 2) Ornithotic pneumonia, the best known example being psittacosis, 3) Rickettsial pneumonias comprising typhus, Rocky Mountain spotted fever and Q fever

Aureomycin and chloromycetin are the first drugs known to be effective against any of the viral pneumonias Aureomycin is apparently specific in the treatment of primary atypical pneumonia, ornithotic pneumonia and the Rickettsial diseases, especially Rocky Mountain spotted fever and Q fever Chloromycetin has a similar effect and is thought to be preferable in typhus infections So far as is known, none of the antibiotics have any influence on influenzal pneumonia The dosage of both aureomycin and chloromycetin has been previously given

Pneumonia Associated with Specific Infections

Tularemia Streptomycin is specific in its effect on tularemic pneumonia The dosage is 2 gms daily for approximately a week

The result is dramatic within two to three days after the start of therapy Aureomycin also has a favorable effect on the course of tularemia In view of the striking results with streptomycin and greater general experience with the drug, the latter should still be the drug of choice

Brucellosis Pulmonary infections are rare complications of brucellosis Aureomycin and chloromycetin are equally effective in the treatment of brucellosis, both appearing to be better than the previously used combination of streptomycin and sulfadiazene

Pulmonary Infections due to Fungi Several antibiotics are effective against the fungi, being both fungistatic and fungicidal *in vitro* Most of them are still in the experimental stage being too toxic for use in man It is quite likely that some of these antibiotics will soon be available

Penicillin is said to be valuable in the treatment of actinomycosis¹⁰ and streptothricosis¹¹ It should be used along with the other well established measures in combating fungus infections Dosage should be large and continued for several weeks

Actidione has been used in cryptococcosis with apparently favorable results

Up to this time, there have been no favorable clinical reports on the use of antibiotics in histoplasmosis, coccidiomycosis or any of the other fungi

Pneumonia of Unknown Etiology

It may frequently be impossible to determine the exact cause of a pneumonic process, particularly early in the course of the disease This often applies to the patient who for one reason or another is unable to get hospital care, or in whom adequate laboratory tests may not be possible Even in a modern hospital, early differential diagnosis between such diseases as viral pneumonia, coccidial pneumonia, Friedlander's pneumonia and tularemia may be difficult at the onset To wait for bacteriological confirmation or to put too much faith in the height of a white count may lose valuable time This is particularly true in Friedlander's and tularemia pneumonia In any seriously ill patient therefore, it is advisable to start at once with both penicillin and streptomycin, and if no improvement takes place within a short time, aureomycin and/or chloromycetin should be added Indiscriminate use of the antibiotics should naturally be deplored as there may be development of sensitization phenomena and resistant organisms However, when there is serious unknown pulmonary disease present combined antibiotic therapy is indicated until the exact diagnosis can be made In this connection, it should be stated that following the use of penicillin in pulmonary infections penicillin-resistant

organisms, chiefly gram-negative bacilli may grow and produce disease after penicillin-sensitive organisms have been controlled.¹² This situation would necessitate the use of streptomycin, providing bacteriological evidence of new infections is found

Diseases of the Bronchi

The antibiotics are of considerable importance in inflammatory diseases of the bronchi. In acute or chronic bronchitis which does not respond to the usual measures, a course of antibiotics should be given, particularly if sensitive organisms are found. Penicillin and streptomycin are the drugs of choice. These are best used by the aerosol method, and in severe infections, particularly in the presence of fever, supplementary parenteral therapy should be added.

In bronchiectasis, penicillin and/or streptomycin should be used for acute exacerbations, secondary pneumonia and in preparation for lung surgery. Both aerosol and parenteral methods of administration are effective. The drugs do not cure the disease, but the amount of expectoration can be considerably reduced, and often may be changed from purulent to a thin mucoid sputum. Periodic courses of antibiotics should be given depending on the character of the sputum.

Lung Abscess

Every case of lung abscess should have a thorough trial with antibiotic therapy. Penicillin is the drug of choice when gram-positive bacteria predominate in the sputum, and streptomycin should be used for infections due to gram-negative bacteria. Large doses of penicillin or streptomycin should be used both parenterally and by the aerosol method. Direct instillation of the antibiotics into the tracheobronchial tree in conjunction with bronchoscopy may prove to be of considerable value. The best results are obtained with the acute lung abscess. In chronic pulmonary abscess, antibiotics should also be used with the other well-known methods of therapy. Prior to operation, several days of antibiotic therapy makes the convalescence much smoother.

A course of aureomycin or chloromycetin may prove to be of value in lung abscesses not improved by penicillin or streptomycin.

Empyema

The organisms most commonly found in empyema are the pneumococcus, streptococcus and staphylococcus. Penicillin is therefore the drug of choice. When gram-negative organisms are present, streptomycin should be used. All acute cases should have a short trial of repeated aspirations and instillations of penicillin. Fifty thousand units of penicillin dissolved in 50 cc of isotonic saline

are instilled daily following aspiration of the exudate. When streptomycin is used, 500,000 units are dissolved in 50 cc of saline. Sterile saline should be used to wash out the pleural cavity if the pus is difficult to evacuate with a needle. Parenteral therapy must be continued throughout. If the infection rapidly improves as evidenced by the character of the aspirated fluid, negative culture and general improvement of the patient, then antibiotic therapy is continued. If however, no improvement takes place within a week's time or if the exudate is thick, immediate surgical drainage should be instituted. Delay of operation may result in a thickened pleura and a non-expansile lung. The intrapleural instillation of streptokinase, a fibrinolytic substance, as suggested by Drs Hillet and Sherry,¹³ liquefies the exudate and fibrin deposits on the pleura, allowing easy removal of the purulent exudate. This procedure in combination with the antibiotics would appear to be the ideal therapy for empyema and may eventually supplant surgical drainage.

Antibiotic therapy is rapidly supplanting all forms of chemotherapy in inflammatory pulmonary disease. There is available at the present time a specific antibiotic for most pulmonary infections, except those due to the smaller viruses and the fungi. It is highly probable that in the near future, the newer antibiotics will prove to be effective against the other hitherto irremediable infections of the lungs.

SUMMARY

Penicillin, streptomycin, aureomycin and chloromycetin are all invaluable in the treatment of pulmonary infections.

Penicillin is the drug of choice in all coccal pneumonias, suppurative diseases of the lungs, bronchiectasis, spirochaetal infections and actinomycosis of the lung. It is best given by the intramuscular route, using 50,000 units of crystalline penicillin G every three hours. When repeated injections are not feasible, 12 hourly injections of 400,000 units of penicillin containing 300,000 units of procaine penicillin G and 100,000 units of sodium or potassium penicillin G should be used. In suppurative lung lesions and bronchial infections, aerosol penicillin should be added, using 50,000 units of penicillin dissolved in 1 cc of saline solution, three times daily, preferably with an oxygen tank. In empyemas, direct daily instillation of 50,000 units of penicillin dissolved in 50 cc saline into the pleural cavity may be curative.

Streptomycin is the drug of choice in gram-negative infections of the lung. It is highly specific for pneumonias and pulmonary infections due to Friedlander's bacillus, *B. tularensis*, *B. pestis*, *hemophilus influenzae* and *E. coli*. It is best given by intramuscular

injection of $\frac{1}{2}$ gram every six hours until the infection is under control. In suppurative diseases of the lungs and bronchiectasis, aerosol streptomycin in conjunction with penicillin should be used.

Aureomycin is the drug of choice in atypical pneumonia, ornithotic pneumonia, tularemic pneumonia, Rocky Mountain spotted fever, Q fever infections and brucellosis. The drug is given orally, using 1 gram every six hours for several days, and then $\frac{1}{2}$ gram every six hours. Bacterial pneumonias not responding to penicillin and streptomycin may respond to aureomycin.

Chloromycetin is the drug of choice in pulmonary infections due to typhus, salmonella group, *E. coli* and brucella organisms. The drug is given by mouth, using 1 gram every four to six hours until improvement takes place, then $\frac{1}{2}$ gram every six hours.

Combined Therapy In pulmonary infections of unknown etiology, it is often invaluable to use both penicillin and streptomycin at once, and if in a short time improvement does not occur, aureomycin and/or streptomycin should be added.

Other Antibiotics Several of the newer antibiotics show great promise in the treatment of hitherto incurable lesions, such as fungus and viral infections. Most of these are still toxic to animals but it is very likely that with further refinements in preparation, they will soon prove to be effective in a still wider range of pulmonary infections.

RESUMEN

En el tratamiento de las infecciones pulmonares la penicilina, la estreptomycin y la aureomicina son de valor inapreciable.

La penicilina es la droga de elección en todas las infecciones neumónicas por cocos, supuraciones del pulmón, bronquiectasias, infecciones por espiroquetas y actinomicosis pulmonar.

Es mejor darla por vía intramuscular usando 50,000 unidades de penicilina cristalina G cada tres horas. Cuando no es posible inyectar con frecuencia puede usarse Penicilina G potásica 100,000 unidades asociada a penicilina procaínica 300,000 unidades cada doce horas. En las lesiones supurantes y bronquiales el aerosol de penicilina usando 50,000 unidades en 1 cc de solución fisiológica tres veces al día puede usarse mediante un tanque de oxígeno. En los empiemas la instilación directa diariamente de 50,000 unidades en 50 cc de solución salina en la cavidad pleural puede curar.

La Estreptomycin es la droga de elección en las infecciones del pulmón por gérmenes Gram negativos. Es altamente específica para las neumonías y las infecciones pulmonares por bacilo de Friedlander, bacilo tularis, peste, hemofilo de la influenza y *E. coli*. Es mejor inyectarlo intramuscular a razón de medio gramo cada seis horas hasta que la infección se domine.

En las supuraciones de los pulmones y en bronquectasias el aerosol de estreptomycina combinado con el de penicilina deben usarse

La aureomicina es la droga preferible en las neumonías atípicas, neumonía psitacosa, tularémica, en la fiebre de las Montañas Rocallosas, en la fiebre Q y en la brucelosis

La droga se usa oralmente dando un gramo cada seis horas por varios días y despues medio gramo cada seis horas Las neumonías bacterianas que no responden a penicilina y estreptomycina pueden responder a la aureomicina

La cloromicetina es la droga preferible en la tifoidea, el grupo de salmonedas, el tifo, la brucelosis y la E coli Se da por via oral un gramo cada seis horas hasta que se presente mejoría y despues medio gramo cada seis horas

Terapéutica combinada En las infecciones de naturaleza desconocida es a menudo util usar tanto penicilina como estreptomycina y si después de corto tiempo no ocurre la mejoría deben usarse la aureomicina y la cloromicetina

Otros antibióticos Varios de los mas nuevos antibioticos son prometedores en el tratamiento de lesiones hasta ahora incurables La mayoría de estas drogas son aun toxicas para los animales pero es posible que su refinamiento las haga utiles en otras infecciones pulmonares

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Trends in the Use of Antibiotics in Thoracic Surgery

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The discovery of penicillin by Fleming initiated studies that have so sharply accelerated the pace of thoracic surgical advance that many articles appearing on the use of antibiotics are obsolete in whole or in part by the time of publication. It must be recognized at the outset that further masses of data must be painstakingly accumulated before clear-cut indications and dosages can be determined. The excellent cooperative studies being carried out in the Veterans Administration and by others under the direction of the Central Streptomycin Committee have presented extremely valuable data on streptomycin, for example, that have been collected in a surprisingly short time. The tremendous accumulated literature on penicillin has gradually clarified over a longer period a number of problems that have beset the surgeon. Certainly there can be no doubt that with the antibiotics the indications for surgery are being constantly broadened, the complications markedly reduced, and the over-all results immeasurably improved.

It seems superfluous to emphasize that antibiotics, on the other hand, cannot be substituted for good surgical technique and sound surgical judgment. The surgeon must recognize the antibiotics as valuable but necessarily limited adjuncts, and must forego the temptation to lean too heavily on them as a crutch. Unfortunately the indiscriminate use of these agents has become far too common. Russell Brock feels that in England, as many observers note here, undue reliance is being placed on antibiotics to cover poor surgery, and to unjustifiably delay needed operative intervention. The long recognized surgical principles of careful selection of cases, of adequate drainage of suppuration, and of thorough debridement remain unchanged, although the clinical and pathological picture is frequently so altered by the antibiotics that the physician can be easily lulled into a false sense of security.

A large number of chemotherapeutic compounds of biologic origin have been introduced since Fleming's work in 1929. Dubos' tyrothricin has a definite but rather limited topical utility. The more recently discovered aureomycin and chloromycetin would seem to have an increasing application in chest disease, as for

example in Friedlander's infections Within the past year at least six additional antibiotics of some promise have been introduced, although the efficacy of these remains to be ascertained One of these, neomycin, may eventually challenge streptomycin in tuberculosis, another, bacitracin, has stimulated encouraging reports regarding its use topically As yet streptomycin, reported by Waksman and his co-workers in 1944, has been the only antibiotic to approach penicillin in its usefulness to the thoracic surgeon

Streptomycin

Streptomycin, though effective against a number of organisms, is of particular interest to the chest surgeon because of the bacteriostatic effect it exerts on the tubercle bacillus, as the studies of Hinshaw, Feldman, and others have well demonstrated A more favorable effect is exerted on fresh exudative and hematogenous tuberculous lesions than on those essentially productive or fibrotic in nature

Two important considerations, toxicity and the development of streptomycin resistance, have posed serious problems The first, toxicity, apparently relates to the streptomycin blood level, while the second relates to duration of treatment Toxic manifestations have been significantly reduced since dosages of one gram per day have been demonstrated to be as effective as the larger dosage schedules previously in use in surgical regimens Apparently a single dose is quite as satisfactory as divided doses, and is probably less toxic Dihydrostreptomycin, now being extensively investigated, would appear to be as efficacious as streptomycin and to give rise to fewer toxic reactions Inasmuch as there has been some doubt thrown on this last contention, there is still question as to whether it will replace streptomycin We have been using one gram of dihydrostreptomycin in two daily doses almost exclusively during the past 15 months, and have encountered no toxic manifestations of serious nature

As to resistance, Dubos has sober-mindedly predicted that streptomycin may well have outlived its usefulness within 10 years The problem can at least partially be met by limiting the period of administration to six weeks or less, and by withholding the drug except in specific indications Inasmuch as the patient all too often reaches the surgeon after his organisms are already streptomycin fast, Beattie and Blades recommend that streptomycin be reserved for use during the operative period in any case which may be potentially surgical

The crux of the problem of indications for streptomycin comes down to the question of when will the patient receive the maximum benefit from the drug, assuming that an adequate course

may well produce permanent resistance. The phthisiologist, whether he be internist or surgeon, must ask himself the question, "What is the over-all plan for this patient?" Both Carr and Benjamin Brock are in agreement that the antibiotic should be withheld until this plan can be formulated.

In preparing patients for collapse therapy, undoubtedly a certain number having fresh exudative disease can, with the aid of streptomycin, be brought to the procedure more safely and rapidly. There is honest question, however, whether this is good judgment. Perhaps reliance on the patient's resistance with the aid of recognized conservative management is the wiser course. We would subscribe to the view that if the patient can be brought to collapse therapy without streptomycin, this should, with few exceptions, be the rule. However should the progress of his disease be such that definitive collapse therapy would otherwise be impossible, he should justifiably receive the drug. How frequently streptomycin is warranted in an attempt to avoid collapse therapy altogether is of course beyond the scope of this discussion.

Obviously it is advisable to determine streptomycin resistance prior to a course of streptomycin if the drug has been previously administered. Experimental work now going on would indicate that the administration of para-aminosalicylic acid with streptomycin tends to delay the emergence of resistance, as well as to enhance the inhibitory effect over that obtained with either drug alone. If however resistance has already been demonstrated by culture studies, the administration of PAS alone will probably afford at least some measure of protection. (Domagk's TB-1 may also be of real usefulness in this regard.)

Although the intramuscular route is admittedly the best mode of administration, three methods of topical application deserve comment. Our own experience in the treatment of endobronchial tuberculosis by aerosol streptomycin was disappointing as were those of other investigators. The work of Samson, Meissner, and others demonstrating that tuberculous endobronchitis is a deep-seated rather than a superficial disease from a pathological standpoint, undoubtedly explains the equivocal results.

Intrapleural use of streptomycin fell into disrepute when first used in tuberculous empyema. In an early report in 1946 Hinshaw, Feldman, and Pfuetze stated that in seven cases of tuberculous empyema in which streptomycin had been injected only one favorable result was obtained. Encouraged by the mention of one of these seven cases in which a bronchopleural fistula had closed, the senior author successfully expanded a case of tuberculous empyema with bronchopleural fistula which had been refractory to repeated aspirations over a period of five months. One gram

of streptomycin was injected intrapleurally daily, after thorough irrigation with normal saline. The bronchopleural fistula was closed within two weeks, and prompt re-expansion of the lung followed. Three conditions would have to be present to duplicate such a result: (a) a small bronchopleural fistula, (b) the absence of secondary organisms in the empyema, and (c) the absence of a thick fibrin cortex over the lung. In most cases decortication would be preferable.

Various thoracic surgeons have advocated the use of streptomycin intrapleurally following resection and have felt that it provides appreciable protection, particularly when there has been gross contamination of the pleural space. The efficacy of such a procedure is difficult to evaluate in view of the attendant use of streptomycin intramuscularly; the rationale of the procedure, however, is sound. A third topical use of streptomycin in tuberculous sinuses probably needs further investigation. Intramuscular use certainly seems more logical than topical application, in view of the fact that the latter probably cannot reach the more deeply involved tissues.

In the light of our present knowledge of streptomycin in tuberculosis, certain operative usages deserve consideration.

Extrapleural Thoracoplasty It must be admitted from the figures accumulated by the Veterans Administration and others, that the use of streptomycin prophylactically in thoracoplasty undoubtedly reduces the postoperative morbidity, the incidence of spread and reactivation, and the occurrence of wound infection. On the other hand the technique of thoracoplasty has been so well standardized in the hands of competent thoracic surgeons that complications at the present time are comparatively rare. In the figures from most thoracic clinics spreads or reactivations occurred in from 3 to 6 per cent of cases. This relatively low figure is due, no doubt, to a number of factors: the careful selection of cases, improved surgical and anesthetic techniques, and better postoperative care. In our own series the incidence of significant spreads or reactivations has been below the 3 per cent figure during the past five years. We feel that operating on the thoracoplasty patient in the afternoon, after he has had an opportunity to raise his sputum adequately in the morning, is an important factor in the low incidence of this complication. We have used closed anesthesia, rather than intratracheal as advocated by Murphy and Walkup, who feel that the maintenance of a good bronchial toilet is essential. From the Veterans Administration collected figures, Murphy has reported a reduction in occurrence of spreads from 5.6 to 2.0 per cent by virtue of streptomycin protection in a consecutive series of 1347 thoracoplasty stages. Roughly

half of the group received streptomycin, while the other half served as controls. Wound infections in this same group were reduced from 24 to 11 per cent. These figures would seem to be statistically significant, although the factors heretofore mentioned have in the hands of some surgeons kept the complications to a comparable figure prior to the advent of streptomycin.

If apparently adequate thoracoplasty fails, as it will in 20 to 35 per cent of cases, the only two procedures feasible for this group with residual cavitation are lobectomy and cavernostomy. Inasmuch as present figures would indicate that streptomycin protection is practically mandatory in resections for tuberculosis, and in the closure of cavernostomy sinuses, it would appear poor judgment to use streptomycin routinely in thoracoplasty in an attempt to benefit less than 6 per cent while jeopardizing the chances of the 20 to 35 per cent who well may need streptomycin protection later and yet be unable to avail themselves of the drug because of resistance. Since it has not been demonstrated that the percentage of cavity closure is higher with streptomycin than without, it is more logical to avoid routine administration of the drug in thoracoplasty, and to use it instead to treat the complications of spread or wound infections in those few cases where they do appear, and to protect the occasional substandard risk. Patients in the older age group, to illustrate, might be justifiable risks for thoracoplasty with the aid of streptomycin, but would not be feasible candidates for resection in any event. It should be mentioned that the Veterans Administration protocols have abandoned the use of streptomycin routinely in thoracoplasty.

If the surgeon has decided that streptomycin should be given, as in cases of severe endobronchial tuberculosis, for example, it is important that the operation be so timed that the patient can be carried through all stages of the procedure before streptomycin resistance would in all likelihood develop.

Of course if a Schede thoracoplasty is performed, and actual tuberculous tissue incised, streptomycin is no doubt indicated. Samson feels that if the thoracoplasty is being done over a mixed empyema streptomycin should be given throughout. He also recommends administration with anterior thoracoplasty stages prior to insertion of a Monaldi catheter in patients with tension cavities, citing that Alexander and Welles both have reported a disproportionate number of spreads in this group. In our own experience with eight cases where the time interval between the preliminary anterior stage and the insertion of the catheter was reduced to a week or less, no spreads occurred but tuberculous wound infection developed several months later in two cases, or 25 per cent, in spite of adequate preoperative and postoperative streptomycin.

We feel the interval between the two procedures was too brief, and have since lengthened it

Other Collapse Therapy While results in most types of collapse therapy are better with streptomycin than without it, the considerations pointed out above would constitute serious deterrents to the use of streptomycin. Specifically we feel that in closed pneumonolysis no streptomycin should be given unless complications develop. Open pneumonolysis, on the other hand, might need streptomycin coverage for at least a short period because of the more extensive operative measures demanded. Extrapleural pneumothorax might occasionally warrant streptomycin on an individualized basis. As to pneumothorax, it has not been our experience that tension cavities failing to close with pneumothorax could, in many instances, be converted to cavities with adequate bronchial communication by the use of streptomycin alone.

Cavernostomy In the usual Eloesser flap cavernostomy done in two stages we do not feel it is necessary to administer streptomycin at either stage. However when closure becomes necessary streptomycin is of unquestioned value. Murphy has pointed this out, and under streptomycin protection has closed over 20 cavernostomies, securing primary healing in over 90 per cent. Although our own experience has not been so satisfactory, we heartily subscribe to using streptomycin in such instances. The dosage used has been 1 gram a day for a week prior to operation, and for two or more weeks postoperatively. Because of the secondary infection invariably present, intramuscular penicillin G potassium in doses of 50,000 units or more every three hours is administered.

Pulmonary Decortication In this procedure, which is still considered of controversial value by some, we feel that protection of the patient by streptomycin is highly desirable, and is mandatory if decortication is being done following tuberculous empyema, or while tuberculous infection of the pleura is present. If a mixed infection is present large doses of penicillin G potassium up to 300,000 units every three hours may also be advisable, in addition to the usual 1 gram of streptomycin as outlined in cavernostomy closure routines. There have been no wound infections and no spreads in our series of seven decortications for tuberculosis. Six of these are considered to have a good functional result with satisfactory obliteration of the space. The other has a small residual pleural pocket at the cupola. We have followed the policy of continuing streptomycin postoperatively until the temperature has been normal for five days. This in all cases has been less than the period of two weeks suggested in most protocols. We think the use of penicillin intramuscularly both preoperatively and post-

operatively is desirable as a protective measure. Usually one of the repository preparations suffices.

Tuberculous Sinuses The response of tuberculous sinuses to streptomycin therapy has been spectacular, inasmuch as this type of lesion notoriously persisted for many months or years before the advent of streptomycin. Brock reported a series of 60 sinuses in 12 patients with excellent results, and believes that healing can be obtained in 95 per cent of sinus cases treated with streptomycin where free surgical drainage exists. Relapses, as reported by some observers, are usually due to the failure to carry out adequate debridement on all sinuses and infected wounds before beginning streptomycin. If all tuberculous tissue can be excised, and relatively clean tissue approximated, the results are, as Brock has stated, amazingly satisfactory. As in cavernostomy, the addition of penicillin to the chemotherapeutic regimen is highly desirable.

Pulmonary Resection The evidence strongly supports the conclusion of Murphy and of Moore that streptomycin be considered mandatory before and after every pulmonary resection for tuberculosis where the organisms are not streptomycin fast. Prior to its use as an adjunct in tuberculous resections, 600 cases were reported in the American literature. In this series the total operative mortality was 25 per cent, empyema 12 per cent, and bronchopleural fistula 8 per cent. Overholt reported 104 cases of pulmonary resection without the use of streptomycin between March 31, 1944 and April 5, 1946, with 15 per cent mortality. Bailey had a 25 per cent mortality in 100 pulmonary resections without the use of streptomycin, and noted 18 per cent spreads, 8 per cent bronchopleural fistulas, and 11 per cent empyemas. In 100 comparable cases Bailey used streptomycin and reported an operative mortality of 14 per cent with only 1 per cent tuberculous spreads, 1 per cent bronchopleural fistulas, and 2 per cent empyemas. Figures from the Veterans Administration showed a drop in operative mortality to 4.5 per cent following the use of streptomycin in contrast to the pre-streptomycin rate of 25 per cent.

At the Veterans Hospital at Oteen, North Carolina, 69 pneumonectomies and 64 lobectomies have been done with streptomycin protection. In the pneumonectomy group the operative mortality has been 6.1 per cent, the non-operative 4.5 per cent, the incidence of spreads 6.1 per cent, of bronchopleural fistulas 13 per cent, and of empyemas 3 per cent. In the lobectomy group the operative mortality has been 5.4 per cent, the non-operative 1.7 per cent, spreads 3.6 per cent, fistulas 9 per cent, and empyemas 3 per cent.

When these figures are contrasted with the pre-streptomycin

group of 600 cases reported in the literature, there can be little doubt that streptomycin is a significant factor in the improvement.

At the present time the Oteen group is running a controlled series of resections, giving alternate cases 1 gram of streptomycin one week preoperatively and two weeks postoperatively, the regimen that most thoracic surgeons are recommending. The remainder of the patients serve as controls and receive no streptomycin. The obvious purpose of the study is to answer the question whether such factors as improved operative techniques and better selection of cases might be the ones responsible for the reduction in complications, rather than the streptomycin. The results of this important investigation will not be apparent for at least another year.

Bogen feels that it is wiser for surgeons to withhold streptomycin during and for a short time following resection until evidence of spread or wound infection has actually been observed, whereupon adequate treatment with streptomycin for at least a month or six weeks might better be expected to care for the complication.

Our feeling is that with the present data at hand streptomycin is the responsible factor for the improved statistics. There are undoubtedly other factors, such as the Overholt face down position and improved bronchial closure, that have contributed to the reduction in mortality rate and incidence of complications. We cannot, however, reconcile the denying of streptomycin to patients undergoing as serious a procedure as resection.

There has been some question in our minds as to whether a shorter period than one week of streptomycin preoperatively would not be fully as effective, at least in those cases where the exudative component is of little significance. By the same token we must admit that the postoperative administration for two weeks is also an arbitrary figure, and may, if anything, be too brief to give adequate protection. Careful evaluation of latent spreads in a large group of patients will be necessary before the full value of the drug is apparent. Without question it will always be necessary for the surgeon to exercise individual judgment in considering each new candidate for resection. Because of the non-tuberculous bronchitis undoubtedly present to at least some extent in every case of tuberculosis where the disease is sufficiently far advanced as to demand resection, we have used both nebulized and intramuscular penicillin to prepare patients for operation. As to the continuance of penicillin following resection, we have used the same criterion as in non-tuberculous resections, continuing the penicillin for a period of several days after the return of the temperature to normal. This of course can be done with more

assurance because the surgeon is dealing with infections not having the complex chronicity of tuberculosis

Pericardectomy Certainly in those cases where the tubercle bacillus is suspected as the causative agent for the constrictive pericarditis, streptomycin is highly desirable. If the tuberculous infection has adequately subsided and stabilized, the same regimen of streptomycin for a week preoperatively and two weeks postoperatively should be adequate. It well may prove feasible to operate on constrictive pericarditis in a much earlier phase now that streptomycin is available. In such instances it would seem more logical to administer streptomycin for a period of at least three weeks before operation, and to continue it for another three weeks after operation. As in other surgical procedures, the surgeon should always plan his operations for a time when there is at least reasonable assurance that streptomycin resistance cannot yet have developed.

Penicillin

The fact that penicillin is effective against a large number of organisms, principally the gram-positive group, implies that studies should be made to determine penicillin sensitivity before the drug is administered on an empiric basis. The same rule of course applies to all antibiotics. Our impression is that penicillin is being given far too frequently. Fortunately the organisms to be combated are as a whole more short-lived than the tubercle bacillus, and the development of resistance of less importance.

At low levels penicillin is bacteriostatic, at higher levels it is bacteriocidal. For susceptible bacteria there is a minimum concentration that retards growth, a somewhat higher concentration that kills the organisms faster than they multiply, and a still higher concentration that kills them at a maximum rate. Thus the present tendency toward larger doses is a valid one. The ideal therapeutic blood level implies a concentration of penicillin that will kill the most bacteria in the shortest possible time. Since penicillin G potassium will give the highest blood levels, it is probably the most valuable preparation for the surgeon, at least in combating the common postoperative complications susceptible to the drug. We feel that even though the blood level may be raised above the maximal effective level by larger dose schedules, the excess penicillin is not wasted inasmuch as it tends to keep the blood level within the therapeutic range for a longer time and insures a higher tissue level in areas having a poor blood supply.

The so-called repository penicillin preparations, designed to provide prolonged effective blood levels, have proved satisfactory.

in our experience for preoperative prophylaxis in those cases in which infection is relatively minimal. In such instances a single daily dose of 400,000 units of the repository preparation is given for a period of one or two days preoperatively. In many patients where the chances of postoperative pneumonia and other infectious complications are small, the same dosage may be continued postoperatively until the temperature is normal for several days.

If on the other hand massive active infection with penicillin-sensitive organisms is present, we use dosages as high as 300,000 units of penicillin G potassium at three hour intervals. Recent work at Bellevue Hospital suggests that even higher doses are sometimes indicated.

We have been particularly interested in aerosol penicillin in the treatment of chronic chest disease, having used it in over 500 cases, and have felt it is of real help in preparing patients for surgery. Admittedly low and ineffective blood levels are obtained with aerosol penicillin. However the purpose of this type of therapy is not to obtain high blood levels, but to obtain high levels on the bronchial mucosal surface. A number of investigators have demonstrated that the bronchial tree can be at least temporarily sterilized after a few days of aerosol therapy. Since this therapy can be timed to carry the patient over the crucial period of surgery itself, particularly in those cases where the bronchus is opened as in resection, the aerosol route should provide considerable protection. We feel rather strongly that bronchoscopy prior to the use of the aerosol antibiotics greatly increases the effectiveness of the inhalation therapy. Siltzbach advocates intratracheal instillation, and claims a 50 per cent drop in sputum volume within 24 hours. He contends the method is of great value in preparing bronchiectatic patients for lobectomy.

Intrapleural administration of penicillin in our practice is largely limited to instillation following routine pneumonectomy and irrigation following contaminated resection. It might be added that careful follow-up is necessary in the latter type of case lest the surgeon be led to consider the contaminated field as having been sterilized rather than rendered temporarily bacteriologically static.

We do not as a rule treat empyema by intrapleural instillation unless the infection is a very early one. Once the pus has thickened, it is far more satisfactory to perform a simple open thoracotomy than to subject the patient to a long series of repeated thoracenteses, with extended expensive hospitalization. There are however exceptional instances in which the use of intrapleural penicillin in empyema may be of great value. We have had the experience of sterilizing three pneumothorax spaces contaminated with penicillin-susceptible organisms without having to reexpand

the pneumothorax to obliterate the space. We have had an equally good result in the case of a right pneumonectomy for lung abscess. Although two courses of penicillin instillation were necessary, this patient escaped without drainage of his empyema space, and continues well to date some five years following his resection. These are admittedly isolated usages.

The problem of penicillin usage can probably best be clarified by considering several disease categories in which it is of value.

Bronchiectasis In those patients who are being prepared for surgery, bronchoscopy is the first step of the regimen. This is followed by an intensive course of expectorants and postural drainage and antibiotic therapy. The secretions obtained at bronchoscopy can, through smear and culture, provide an accurate picture of the bacterial flora involved. Penicillin, at the rate of 25,000 units, is administered by the aerosol route every three hours during the day for 16 inhalations or more. We add six drops of prothricin to each dose for the shrinking effect and for the action of the tyrothricin on the usually complex endobronchial flora. We have felt that bacitracin combined with a vasoconstrictor may prove superior to prothricin. If streptomycin-sensitive organisms have been found, streptomycin is added to the inhalations. This is doubly important since some of these streptomycin-sensitive organisms may elaborate a penicillinase inhibiting the action of the penicillin.

With the above measures the sputum volume can usually be significantly reduced, and the general condition of the patient considerably improved. Inasmuch as resection for bronchiectasis is almost always an elective procedure, the operation should be postponed until the patient is optimally prepared.

We also order repository penicillin for two or more days preoperatively, or use regular penicillin if considerable infection is present. Postoperatively regular penicillin is administered every three hours. We have rarely seen infection develop in an atelectatic area prior to relief of the block when these measures are carried out.

As previously mentioned penicillin is instilled into the pleural space after removal of the lung, and is sometimes used for irrigation via the intercostal drainage tube in cases of lobectomy and segmental resection. At the time the intercostal tube is removed, 100,000 to 200,000 units of penicillin is injected into the pleural space. In our experience the incidence of empyema has been exceedingly small, as has that of bronchopleural fistula.

Kay, Meade, and Hughes have reported an outstanding series of 220 lobectomies, largely for bronchiectasis, with but one death. All were protected with penicillin both pre and postoperatively. White et al, in a series of 41 patients undergoing lobectomy and

pneumonectomy found no empyemas in the group receiving penicillin, while the pre-penicillin group had 60 per cent empyemas. In the suppurative category all of the control group receiving no penicillin developed empyemas. These investigators point out that penicillin serves to control acute and chronic infection in the pulmonary tissues, and reduces the possibility of postoperative infection. In addition it affords a maximum therapeutic effect at the time the pleura is exposed to bronchial contamination.

Lung Abscess The adequacy of chemotherapeutic and antibiotic therapy depends to an appreciable extent of course on the duration of the abscess as well as on the causative organisms. As in bronchiectasis, we feel that bronchoscopy should be done immediately to promote adequate bronchial drainage. The same smear and culture studies are made. Penicillin G potassium up to 300,000 units every three hours is administered intramuscularly, and aureomycin 500 mg is given every three hours by mouth. If gram-negative organisms are recovered from the bronchial secretions, streptomycin is of course added. Bronchoscopy is repeated as often as is needed to maintain good bronchial drainage; this is felt to be exceedingly important, oftentimes helping to transform an anaerobic lesion into a more easily treated aerobic one. Expectorants and postural drainage are continued. If the patient does not improve promptly following these measures open drainage or resection, usually the latter, is indicated.

It can be emphatically stated that antibiotic therapy is not the solution of the lung abscess problem. In our experience with over 200 lung abscesses, almost as high a percentage came to surgery with antibiotics as without. It is of course admitted that this group has been in far better condition for surgery than the pre-antimicrobial series. There has also been a decided drop in the incidence of lung abscess, undoubtedly due to the fact that antibiotic agents have aborted many potential abscesses. It should be stressed that lung abscess patients should be adequately protected at resection with combined antibiotic therapy, since the incidence of empyema and fistula is appreciably greater in this group than in the bronchiectatic one.

Intrathoracic Tumors All patients undergoing exploratory thoracotomy for intrathoracic tumors can be given repository penicillin for one or two days preoperatively to advantage. Usually aerosol penicillin is given as well. In those cases where no suppurative disease is present, such a regimen will afford adequate prophylaxis against possible bronchial contamination. The repository penicillin is continued postoperatively but regular penicillin substituted if the expected postoperative morbidity is exceeded. Streptomycin is not given unless bacteriological studies reveal streptomycin-

sensitive organisms. As a whole, intrathoracic explorations have been so free of complications in the hands of most thoracic surgeons when adequate antibiotics have been used, that no physician need have qualms about recommending exploration in doubtful lesions.

When postoperative pneumonia is encountered, large doses of penicillin are given intramuscularly without delay. If prompt clearing does not occur, bronchoscopy is performed. With intratracheal anesthesia, antibiotic protection, and bronchoscopy, chest complications can be reduced to a minimum.

Thoracic Trauma In cases of early traumatic hemothorax the patient is placed upon large doses of penicillin G potassium intramuscularly at three hour intervals until thoracenteses bring about obliteration of the pleural space by expansion of the lung. In non-infected organized hemothorax the same regimen is usually continued for the short interval until decortication can be undertaken. At the time of operation additional penicillin is instilled into the pleural space. Regular intramuscular penicillin is continued until satisfactory re-expansion and obliteration have occurred, after which time repository penicillin may be substituted if the temperature is not yet within normal ranges. Where decortication is being done for infected hemothorax or for non-tuberculous empyema, large doses of penicillin G potassium for a few days preoperatively and until the space is completely obliterated postoperatively are of exceeding importance. Prompt re-expansion of the lung with healing by primary intention is usually the rule when vigorous suction has been instituted.

The principles of debridement and primary closure, elucidated during the last war, apply of course to management of chest wall wounds, the main deviation from older techniques being the greater leeway granted the surgeon in primary closure of contaminated wounds and in secondary closure of infected wounds under antibiotic protection.

Surgical Diseases of the Esophagus Before resection is undertaken, the elimination of esophagitis proximal to obstructive lesions will result in less friable tissues for anastomosis, a less dangerous bacterial flora at the operative site, and fewer anastomotic failures. This problem may be managed by attention to oral hygiene, daily irrigation of the esophagus with 100 cc of 5 per cent sodium sulfadiazine, and adequate doses of parenteral penicillin.

At the conclusion of transthoracic operations wherein the esophagus has been opened we routinely introduce 200,000 units of penicillin and 1 gram of streptomycin in 20 cc of normal saline in the pleural cavity before closure. If the peritoneal cavity has been invaded a similar solution is placed in the abdomen before

closure of the diaphragm In the postoperative period the patient receives large intramuscular doses of penicillin G potassium, at least 100,000 units every three hours, and is given streptomycin as well This program, together with improved operative techniques, has eliminated pleural and mediastinal infections except in the occasional patient who develops a gross leak at the anastomosis Even these patients may sometimes be salvaged by more vigorous antibiotic therapy and judiciously selected and properly timed drainage procedures followed by secondary repair These principles also apply in treatment of spontaneous, operative, and foreign body perforations of the esophagus

Surgical Diseases of the Heart and Great Vessels Most surgeons have used prophylactic schedules of the antibiotics to cover resections and anastomoses of great vessels and surgery of the heart valves and septa This therapy has apparently been directed at prevention of bacterial implantation on newly created raw surfaces In this field it may be debatable whether antibiotic protection should be purchased at the price of the reported increased tendency toward intravascular clotting produced by the antibiotics

After drainage of suppurative pericarditis, topical application of the proper agent, as indicated by bacteriologic studies, is obtained by introducing the agent in solution by catheter under low gravity pressure around and posterior to the heart after daily gentle separation of new adhesions with the gloved finger Using 1,000,000 units of penicillin in 250 cc of normal saline at body temperature the benefits of lavage and irrigation are attained simultaneously with specific drug therapy This procedure, as well as intramuscular administration of the agent, is continued daily until space obliteration is obtained

Inasmuch as many authorities, as has been mentioned by Troutman and Vincent, now predict a recovery rate of 90 per cent or better in cases of streptococcus viridans subacute bacterial endocarditis uncomplicated by patent ductus arteriosus with the aid of adequate doses of penicillin (up to 20,000,000 units per day) the routine use of the drug in cases complicated by patent ductus is obviously indicated This in spite of the observation of Touroff and Vesell that the blood stream infection has been cured in certain cases in which the vegetations were limited to the heart valves simply by interruption of the patent duct alone Taussig has pointed out that if in such cases sterilization of the blood stream is not immediate, the infection may be overcome with the aid of penicillin

In cases in which the vegetations also involve the vessel wall, as well as the heart valves, the results of interruption of the patent ductus are poor with regard to sterilization of the blood stream

Furthermore the operation is rendered more hazardous because of the increased friability of the vessel wall. In such cases vigorous penicillin therapy is indicated without question.

The utilization of streptomycin in cases of penicillin-resistant strains of streptococcus fecalis is of course warranted, as reported by Guss and others. The addition of heparin is advised in order to prevent local thrombophlebitis.

SUMMARY

Antibiotics have revolutionized thoracic surgery. As yet streptomycin and penicillin far outweigh the other antibiotics in their value to the thoracic surgeon.

Because resistance to streptomycin develops rapidly and is permanent, this antibiotic should not be used indiscriminately, but should be restricted to specific indications. The use of streptomycin as an adjunct in tuberculosis surgery has extended operative indications, and has made possible safer and more effective pulmonary resection, decortication, cavernostomy, closure of tuberculous sinuses, and pericardectomy. The administration of 1 gram a day, in one or two doses, is recommended for periods of six weeks or less.

In the light of present knowledge the use of streptomycin would not seem justified in routine thoracoplasty, inasmuch as complications are already minimal. Its use is rarely justified in other forms of collapse therapy.

Penicillin has proved of particular value in the surgery of bronchiectasis and lung abscess, in thoracic trauma, in exploration for intrathoracic tumors, in esophageal surgery, and in surgery of the heart and great vessels.

The present trend is toward larger doses of penicillin, with penicillin G potassium the preparation of choice in active infection. In surgery, repository and aerosol penicillin are primarily applicable in prophylaxis.

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Aerosol Therapy of Bronchopulmonary Diseases*

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With the advent of the sulfa drug era in modern medicine the treatment of some bronchopulmonary diseases, especially the more common pneumonias, has become successful. This point can be verified by comparing mortality rates and complications before and after the addition of various sulfa drug preparations to the physician's therapeutic armamentarium. Improvement in the technique and results achieved in the treatment of various bronchopulmonary diseases was further enhanced by the discovery of penicillin and streptomycin until, today, the mortality rate and complications in properly managed cases of the commonly encountered lobar and bronchopneumonias are, by comparison, practically negligible. There remains, however, a large group of acute and chronic common bronchopulmonary diseases which have not responded as favorably as one would expect even with the increased utilization of these newer forms of therapy when they are administered by the usual systemic routes. In particular, the results achieved in the treatment of such conditions as lung abscess, bronchitis and bronchiectasis have been manifestly unsatisfactory as a rule. The very nature of the pathologic processes involved in such conditions explains the usual equivocal or actually unsatisfactory results obtained when the treatment is confined to a systemic attack on the disease. When specific and indicated drugs are administered by the various systemic routes, in these instances, it appears that they are unable to penetrate the pulmonary tissue barriers in sufficient quantity to establish effective therapeutic levels at the site of the infection.⁸ Clinicians have long recognized the fact, therefore, that in certain bronchopulmonary diseases a local as well as a systemic attack upon the underlying disease process is an essential prerequisite for the achievement of lasting cures or, at least, palliative results. Consequently, with this thought in mind, various chemotherapeutic agents, especially the sulfa drugs, were administered by nebulization or direct bronchoscopic instillation.¹ By far and large, the results obtained were not encouraging. With the advent of the

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Many of the original illustrations are omitted because of limited space.

various antibiotic agents, however, the aerosol therapy of many usually resistant acute and chronic bronchopulmonary diseases has resulted in truly remarkable and unanticipated successes^{2 3 5-10} Many patients who would have previously been considered as hopeless cases and perhaps relegated to lives of chronic invalidism, and in many instances eventual death, have benefited immeasurably from the increased utilization of antibiotic aerosols administered either singly or in various combinations

The theory and practice of direct topical administration of therapeutic agents in the treatment of certain bronchopulmonary disorders are in themselves quite ancient³ It was only after the advent of antibiotics, however, that the aerosol treatment of certain previously resistant bronchopulmonary diseases could be undertaken with any degree of expected success Innumerable methods and types of apparatus have been recommended by equally innumerable investigators who unhesitatingly claim superiority for their method of aerosol administration The literature on the subject of aerosol therapy is not only voluminous but also somewhat confusing Consequently, many patients have been deprived of the acknowledged benefits of this form of therapy because a large number of general practitioners, internists and other physicians interested in the treatment of bronchopulmonary diseases have considered the procedure too complicated, theoretical or expensive for successful implementation in their own practices The purpose of this communication is to describe a simple method of administering aerosol therapy, and to record the experiences acquired, problems encountered and results achieved in the treatment of various bronchopulmonary disorders in a large group of patients

Apparatus The Vaponefrin nebulizer (glass) was used exclusively in the treatment of these cases The aerosol is vaporized by means of oxygen at a steady flow of four (4) liters per minute At a convenient point in the rubber tubing which connects the oxygen regulator valve and the nebulizer, a glass "Y" tube is inserted The patient is taught to occlude the free opening of the "Y" tube with a convenient finger-tip for a duration of time equal in length to the duration of each inspiratory effort A tight-fitting cork is inserted in the carburetor opening In this manner, nebulization occurs only when the free opening of the "Y" tube is occluded and treatment is thus effected with a minimum of waste and effort The vaporizer spout is introduced to a point slightly beyond the inner border of the lips and the patient inhales the aerosol through the open mouth

In those instances where it is necessary to treat concomitant sinus infections, a glass reduction tube is attached to the spout

of the nebulizer, and the aerosol is delivered directly into each nostril for alternating periods of time corresponding to the duration of each inspiratory effort. The patient is seated in a comfortable position, and the solution (2 cc) is usually nebulized in a period of 30 minutes. For home treatment, manual vaporization may be accomplished with little effort and with encouraging results. As a general rule, it is advisable not to exceed a volume of 20 cc or 25 cc of the solution which is to be nebulized at each treatment. Larger amounts are apt to be tiring to the patient. A few sensitive individuals will complain of vertigo when oxygen is used, but this symptom may be disregarded.

In order to avoid mechanical difficulties encountered because of the occlusion of the small capillary jet tubes in the nebulizer, it is thoroughly cleansed and sterilized immediately following each treatment. After washing the residue of the medication out of the carburetor, it is a good practice to direct a flow of oxygen or compressed air through the nebulizer jet for a short period of time in order to insure absolute patency of the capillary tubing. It is then placed in bichromate cleaning solution until its next utilization. If this technique is followed and if only medications suitable for aerosol therapy are utilized, one will experience little or no difficulty in the operation of this simple apparatus.

Technique and Drugs The bacterial flora of the bronchopulmonary secretions of patients who are considered suitable candidates for aerosol therapy should be determined before treatment is instituted. This can be accomplished easily by examining a Gram stain of a satisfactory specimen of sputum microscopically. Although the exact nature of the offending microorganism or organisms may not be ascertained accurately by this method, it, nevertheless, serves to classify the responsible etiologic agent as Gram-negative or Gram-positive bacteria. This information is usually adequate and facilitates the rapid institution of effective therapeutic measures. The effect of the aerosol therapy upon the bronchopulmonary infection can then be followed by repeated Gram stain examinations of the sputum. If the anticipated therapeutic response is not achieved, then further bacteriologic studies should be carried out in order to identify accurately the offending microorganism.

The non-tuberculous pathogens responsible for bronchopulmonary infections are generally Gram-positive and will usually respond to penicillin therapy. In a small percentage of cases, however, after the Gram-positive organism is eradicated, the bacterial flora will undergo a relative and absolute increase in both the variety and number of Gram-negative bacteria. Although these organisms are commonly considered to be non-pathogenic, as

secondary invaders they are unquestionably responsible for a protracted period of disability and therapeutic failures in many instances. From clinical observation only, it appears that they assume frequently some of the pathogenic qualities of their Gram-positive neighbors. Recent published observations of other investigators tend to support this opinion.^{2,11} To overcome this difficulty and the previous presence of penicillin resistant bacteria encountered in the aerosol therapy of bronchopulmonary disorders, it is then necessary to supplement the treatment with streptomycin. These two antibiotics used in combination can generally handle all of the more common bronchopulmonary infections. When streptomycin and penicillin are used simultaneously, it is advisable not to use the calcium salt of penicillin with streptomycin sulfate since calcium sulfate is precipitated in this solution and interferes with the mechanical efficiency of the nebulizer. The dosage of penicillin employed varies from 25,000 units to 50,000 units per cc and the dosage of streptomycin usually varies from 50,000 units (0.5 gm) to 100,000 units (1 gm) per cc. Normal saline is used in preference to distilled water as a solvent for either of these antibiotics. Although the physician's individual preference may vary concerning this choice, it is the author's opinion that normal saline is less irritating to mucous membranes than distilled water. Additionally, it is felt that crystalline potassium penicillin is the penicillin of choice in this form of therapy. Some patients will be found, in the course of events, who have been previously sensitized to penicillin or streptomycin, or both. In this event, unless the allergic manifestations are alarming, treatment is continued with the assistance of one of the presently available antihistaminic drugs.

In the absence of any of the acknowledged contraindications, the addition of a vasoconstrictor and decongestant agent to the aerosol solution has been a routine procedure in the treatment of these patients. More recently it has been our practice to use those preparations which have an added amount of thyrothricin* in order to obtain the additional antibacterial effects of this antibiotic. In this manner it is possible to relieve the edema and spasm of the bronchial tree which are commonly associated with bronchopulmonary disorders. The disturbing symptoms which accompany these pathologic changes are noticeably benefited by the addition of a suitable vasoconstrictor and decongestant agent. Furthermore, the presence of thyrothricin, in our experience, usually prevents the rapid multiplication of the Gram-negative bacteria and precludes the use of supplementary streptomycin therapy to

*Sharp & Dohme's Prothricin, and Wyeth's Edryl

combat this complication * This precautionary measure not only serves as a valuable prophylactic measure clinically, but also helps to conserve the patient's economy In some instances where the spasm and edema are marked and do not readily respond to this form of therapy, the utilization of adrenalin 1:100 in the aerosol solution may become necessary In the treatment of asthmatic individuals and those suffering from emphysema, this is a common practice One cc of either prothricin, edryl, vaponefrin or adrenalin 1:100 are usually employed in each treatment These agents can be used as solvents for penicillin or streptomycin in order to decrease the volume of the aerosol solution The latter practice is helpful in the treatment of those patients who operate the nebulizer manually The amount of effort required to nebulize large volumes of aerosol is tiring and occasionally predisposes to an uncooperative patient

Although this communication is designed primarily to stress the use of penicillin and streptomycin aerosol therapy, one cannot neglect to mention briefly in passing that many other drugs can be prepared in suitable solution for aerosol therapy For example, certain sulfa drug preparations are quite suitable for this purpose although the results obtained are inconstant Suitably prepared solutions of aminophyllin may be utilized in attacks of asthma, and the author has used iodide preparations in the treatment of fungus infections By means of the aerosol apparatus it is also possible to prepare patients for radiopaque studies of the bronchial tree and pulmonary segments This can usually be accomplished by the nebulization of as little as 2 cc of a 4 per cent cocaine solution with or without added adrenalin Complete and dependable anesthesia of the tracheobronchial mucosa is the rule with this method and satisfactory bronchograms are obtained with uniform regularity

Method of Treatment—General Considerations The number of daily treatments, length of treatment and the dosage of the antibiotic agent used depend upon the nature and severity of the illness Initially, the more serious cases are treated four times daily The number of daily treatments and drug dosage should be adjusted frequently to parallel the clinical progress in each case Besides antibiotic aerosol therapy, indicated general and symptomatic measures in the treatment of each disorder should not be neglected Many patients require large doses of expectorant cough mixtures in order to loosen the tenacious bronchial

*Since the preparation of this manuscript we have found the use of Soluthricin, 2.5 per cent (Sharp and Dohme), very effective for this purpose and non-toxic From 0.06 cc to 0.1 cc may be employed per cc of aerosol solution

secretions The author has found Brown's Mixture with added ammonium chloride effective in producing this result In other cases, syrup of hydriodic acid was utilized successfully Aside from its expectorant qualities, it has been found equally useful as a palatable prophylactic and therapeutic measure in the treatment of some primary and secondary fungus infections The type of expectorant medication used is, nevertheless, purely a matter of individual preference and patient reaction More important is the daily inspection of the quantity and nature of the sputum which determines the efficacy of the preparation used Expectorants should be administered in the largest tolerated dosage in order to achieve the maximum therapeutic benefit

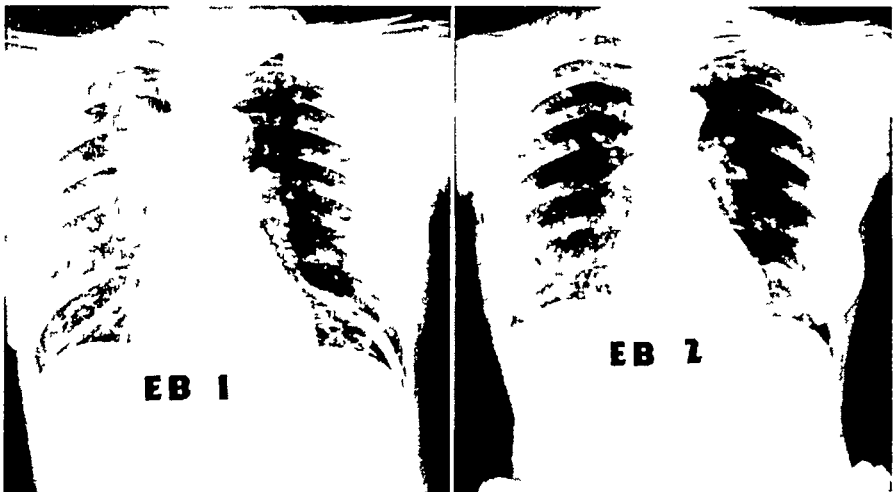
Those individuals suffering from bronchiectasis and lung abscess should be carefully instructed in the technique of correct postural drainage Of course, in those patients who are chronically ill and debilitated, the state of nutrition must receive careful attention, and the possibility of blood transfusions in these individuals should always be considered Likewise, a large number of these patients experience difficulty in obtaining the required amount of rest and sleep and, for this reason, adequate amounts of sedative drugs should be used liberally Agents which are primarily intended to suppress the cough reflex, on the other hand, should be used in the minimal effective dosage and only when absolutely necessary In many cases the use of aerosol therapy by itself will be sufficient to control or cure the underlying bronchopulmonary disorder Until we were able to demonstrate the unquestionable efficacy of aerosol therapy in these cases, it was utilized primarily as an adjunct type of treatment, and patients received large doses of various chemotherapeutic and antibiotic agents concomitantly by the systemic route It was soon found, however, that in numerous instances the simultaneous systemic administration of chemotherapeutic and antibiotic agents was clinically unnecessary and an economic waste Once the systemic manifestations of the illness are adequately controlled, specific drug therapy can be confined exclusively to the aerosol route of administration

In addition to following each patient's progress by the usual clinical signs and symptoms, frequent x-ray examinations of the chest and microscopic examinations of properly stained bronchopulmonary secretions should be evaluated at regular intervals These precautions are necessary in order to manage each case intelligently and effectively As the physician gains wider experience in the use of aerosol therapy, he will be emphatically impressed with the individual variations in each disease and in each patient Reliable indices of the clinical progress in cases of bronchiectasis and lung abscess can be maintained by careful obser-

vation of the nature and amount of the daily sputum (Case 5) When the physician is satisfied that the disease has been adequately controlled, patients can be instructed in the manual use of the nebulizer and permitted to follow the prescribed treatment at home In cases of lung abscess, frequent follow-up x-ray examinations are imperative because of the notorious tendency toward recurrence even months after the infection has been apparently controlled (Case 6) If, in properly selected cases, the expected therapeutic response with aerosol therapy is not achieved in a reasonable length of time, especially in the case of lung abscesses, bronchoscopic examination and aspiration of the bronchial tree are indicated

Case Histories The following case histories and roentgenograms are presented in an effort to demonstrate the results achieved and problems encountered in a representative group of patients suffering from common varieties of resistant, acute and chronic, bronchopulmonary disorders treated with aerosol therapy

Case 1 EB, a 65-year-old white spinster For 20 years suffered from severe sinusitis and bronchitis with frequent acute exacerbations The patient's condition had deteriorated steadily over this long period of years until she was practically a bedridden invalid Among the innumerable therapeutic measures tried, systemic administration of various sulfa drug preparations, penicillin and streptomycin in large amounts and for prolonged periods of time either individually or as combined therapy, likewise, failed to arrest the steady progress of the disease When first seen several million units of both penicillin and streptomycin together with large amounts of sulfadiazine had been administered systemically for several weeks without any appreciable effect upon the course of the illness The roentgenogram showed evidence of patchy pneumonitis (Fig EB 1) Clinically, she had an almost continuous exhausting and productive cough, and at times temperature spikes as high



CASE 1

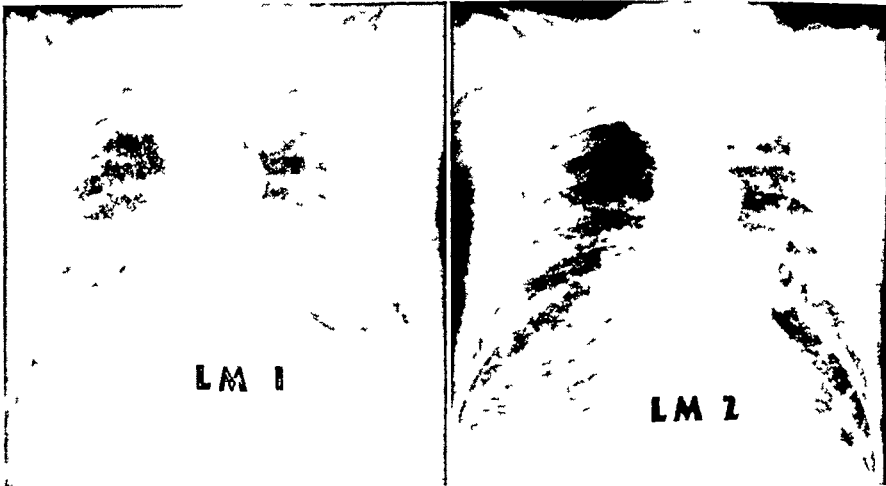
as 103 degrees F (oral) were recorded. Aerosol penicillin and streptomycin therapy by nasal and oral routes produced a rapid subsidence of all symptoms and signs. Systemic administration of all chemotherapeutic and antibiotic agents was discontinued after 48 hours. A roentgenogram of the chest (Fig EB 2) 10 days after the institution of aerosol therapy showed remarkable clearing. This improvement has been maintained for the past 14 months. Infrequent minor relapses are rapidly controlled by penicillin aerosol therapy. During this period of time, she has gained much weight and strength and is now able to carry on a practically normal existence.

Comment The author prefers the descriptive terminology of bronchosinus disease as a label for the frequent combination of sinusitis and bronchitis. From the therapeutic standpoint it is really unimportant to determine whether the sinusitis preceded the bronchitis or vice versa. This controversial problem, in itself, has long been the subject of numerous investigations but is still undecided. The simultaneous treatment of both conditions is the important therapeutic consideration in this illness. Both areas of infection must be controlled in order to obtain satisfactory and lasting results. Lingering infection in either area predisposes to reinfection of the other. Furthermore, in order to avoid serious relapses, aggressive antibiotic aerosol therapy should be instituted at the first sign of recurrence. In this particular case, as well as in many other bronchopulmonary disorders, the rapidity of roentgenographic resolution of the disease process does not necessarily parallel the clinical progress of the disease. Frequently, abnormalities in serial roentgenograms of the chest can be detected long after the patient is completely relieved of all clinical signs and symptoms. In bronchosinus disease the clinical improvement, as a rule, is unusually rapid and easy to sustain. Nevertheless, in order to obtain optimal results from the use of aerosol therapy in bronchosinus disease, treatment should be energetic in the earliest and acute stages of the illness. Many cases of otherwise intractable chronic bronchosinus disease could be avoided in this manner.

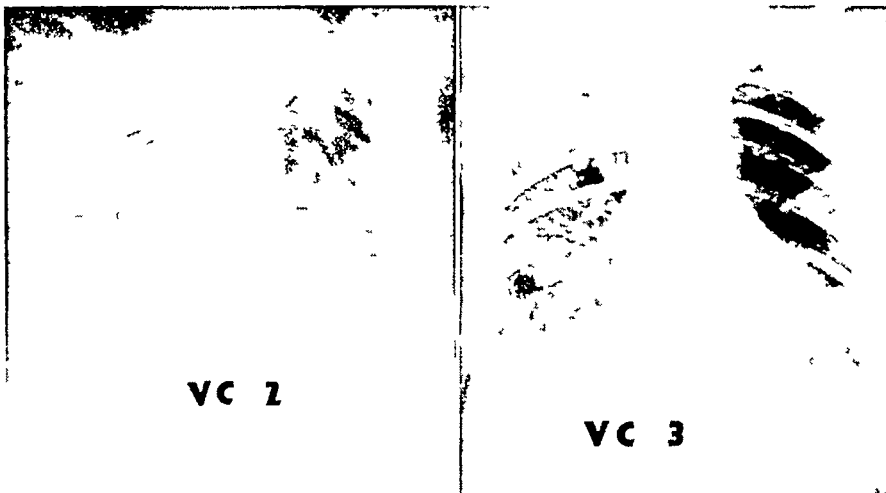
Case 2 LM is a 66-year-old white male who worked in a foundry practically all of his employable years. He was retired because of disabling silicosis. During the past 10 years there were numerous episodes of superimposed bronchopneumonia. The therapeutic effectiveness of various sulfa drugs and antibiotic agents became less satisfactory with each recurrence until at the time of the most recent bronchopneumonic complication (Fig LM 1) response to systemic therapy was practically negligible. Aerosol penicillin therapy together with adrenalin 1:100 produced remarkable alleviation of all clinical signs and symptoms. Within six days there was marked improvement in the roentgenogram (Fig LM 2). However, his general condition deteriorated rapidly and he died from respiratory failure during the course of his hospitalization. Necropsy substantiated the clinical diagnosis.

Case 3 VC, a 52-year-old white female Radical mastectomy had been performed for cancer of the right breast. Additionally, received intensive radiation therapy. Subsequently, developed radiation pneumonitis. The systemic administration of large doses of sulfa drugs, penicillin and streptomycin not only failed to control the illness, but there was actual progression of clinical signs and symptoms (Fig VC 2). Four days after aerosol penicillin therapy was instituted there was marked clinical and x-ray evidence of improvement (Fig VC 3). Extensive metastatic lesions demonstrated at autopsy, nevertheless, were responsible for her eventual death.

Comment In these instances, although treatment failed to save the patient's life, death in each case was the result of the underlying disease process and not the secondary infection. The clinical improvement and the increased comfort to the patient



CASE 2

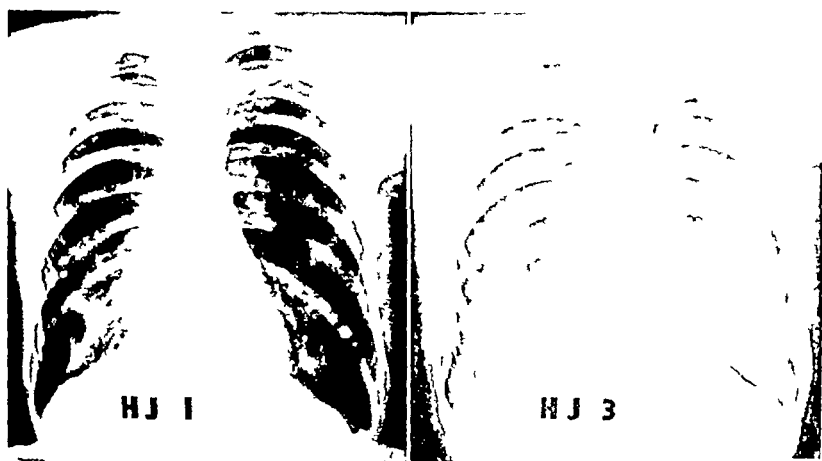


CASE 3

warranted the use of aerosol therapy. Systemic administration of various drugs was useless because the blood supply to the involved area was completely disrupted and rendered inadequate by the primary condition. This type of disease is an excellent indication for aerosol therapy.

Case 4 H J, a 45-year-old white carpenter was treated for "flu" in November, 1946. Although the patient returned to his usual occupation after several weeks of illness, recovery was never complete. There was a persistent productive and annoying cough with daily small elevations of temperature. A roentgenogram of his chest on March 31, 1947 revealed a dense area of infiltration in the para-cardiac area of the right lower lobe, which extended to the diaphragm (Fig HJ 1). Bronchograms were not obtained because of the patient's refusal to submit to the procedure. After a careful review of this patient's illness, it was decided that he was suffering from pseudo-bronchiectasis. The original diagnosis of "flu" was changed to primary atypical pneumonia of undetermined etiology. Systemic sulfa drug and penicillin treatment had failed to influence this complication of the original disease and the patient continued to lose weight and strength. Nine days after the institution of aerosol penicillin and streptomycin therapy there was marked clinical and roentgenographic improvement. Three and one-half months later re-ray of the chest showed almost complete resolution of the original infiltration (Fig HJ 3). Aerosol penicillin and streptomycin therapy in this case was administered for about 10 days, and there has been no recurrence of the disease during the past year.

Comment The term pseudobronchiectasis was first used by Brian Blades.⁴ Although many investigators question the existence of this entity, the author shares his opinion without reservation. Since the publication of Blades' original observation, numerous cases of primary atypical pneumonia of undetermined etiology have been encountered in which the syndrome of pseudo-



CASE 4

bronchiectasis was recognized in the course of a protracted convalescence. The results obtained with aerosol therapy in this case again demonstrate the superiority of this form of treatment in selected cases.

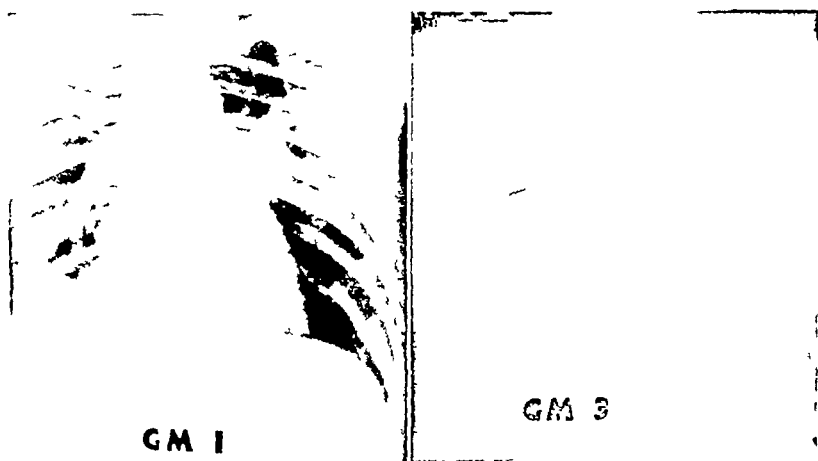
Case 5 L.H., a 37-year-old white male was told that he had bronchiectasis five years previously. Cough and expectoration of foul smelling purulent material continued unabated and increased in spite of many types of treatment. When first seen he was raising between 12 and 16 ounces of sputum daily. A bronchogram revealed the existence of dilated and distorted bronchi in both lower lobes. No attempt was made to outline any other pulmonary segments. Aerosol penicillin and streptomycin therapy, together with postural drainage and other general supportive measures, produced marked improvement in this patient's condition. The quantity of sputum decreased rapidly until, at the end of 12 days of treatment, he was raising only from 15 to 20 cc. of a watery type sputum. Only rare bacterial organisms were demonstrated by direct smear and stain.

Comment The use of aerosol antibiotic therapy in long-standing cases of bronchiectasis is not intended as a curative measure. It is used primarily as a palliative procedure only to achieve symptomatic improvement. Many patient's lives have been made more pleasant since the advent of this form of therapy. Additionally, aerosol antibiotic therapy is valuable as a preoperative measure in the preparation of these patients for lobectomy or pneumonectomy.^{6,9} Aerosol therapy preoperatively is indicated in all patients who are candidates for major pulmonary surgical procedures. The routine preoperative aerosol preparation of these patients will generally minimize the surgical risks and complications. Control of the pulmonary infection will improve the general clinical status and make patients more suitable candidates for surgery. Many patients who, in the past, would have been denied the benefits of surgical therapy because of their debilitated condition can now be converted to suitable candidates for surgery. Satisfactory tracheobronchial anesthesia prior to instillation of lipiodol in this case was obtained after aerosol administration of 2 cc. of a solution of cocaine 4 per cent with a small amount of added adrenalin. Although this patient was apprehensive, a satisfactory bronchogram of the desired pulmonary segments was procured. This method of obtaining effective and complete tracheobronchial anesthesia has been used successfully in many patients, not only preparatory to bronchographic studies but also in preparation for bronchoscopic examinations. The cough reflex is usually effectively abolished, and a satisfactory anesthesia is obtained with a minimum of anesthetic agent and technical effort. Even apprehensive individuals are able to cooperate and

satisfactory bronchograms are the rule because of the total type of anesthesia

Case 6 G M, a 50-year-old white male was found to be suffering from a lung abscess six months following the extraction of several teeth (Fig GM 1, recumbent portable x-ray) Although he was quite ill most of this time, he did not seek medical treatment. Instead he drank about one pint of whiskey daily to control his symptoms. Large systemic doses of sulfa drugs and penicillin failed to produce any clinical improvement. Ten days after the institution of aerosol penicillin therapy together with other general measures indicated in the treatment of pulmonary abscess, roentgenographic, as well as clinical improvement was marked. Two months later there was no roentgenographic evidence of the original pulmonary abscess (Fig GM 3). However, a chronic mild cough productive of small amounts of sputum persisted. This patient was never very cooperative and soon after discharge from the hospital abandoned all recommended treatment. Nevertheless, his progress remained satisfactory until one year later. At that time two thin-walled cavities reappeared at the site of the original lesion. He again refused medical attention and has not been heard from since.

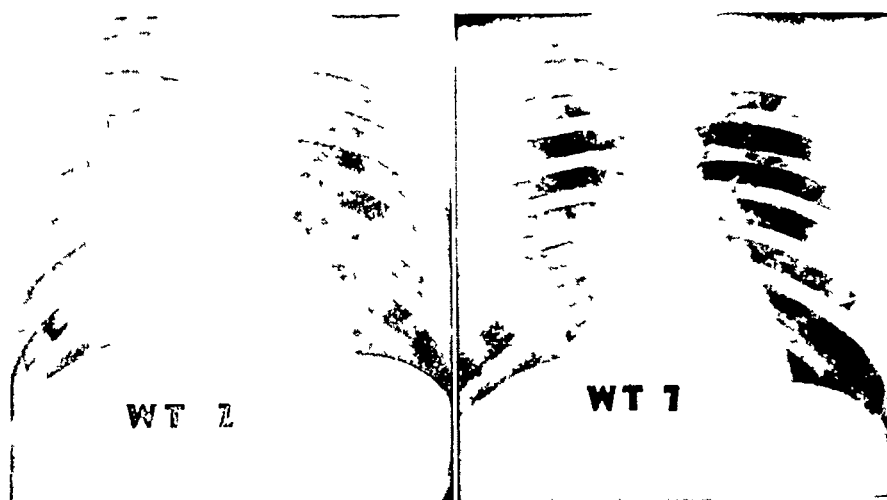
Comment Ordinarily one would not expect a pulmonary abscess of this long-standing to respond to conservative medical management. Actually, in this particular case, aerosol penicillin therapy was instituted with the express purpose of preparing this patient for lobectomy. The unexpected clinical and roentgenographic improvement, however, precluded the necessity for surgical intervention. Recurrence of the original abscess in this case demonstrated the importance of repeated frequent serial roentgenographic chest examination of all patients in whom apparent cures are obtained. Although therapeutic results are more consistent and satisfactory in the acute lung abscesses, occasional permanent



CASE 6

successes in the chronic variety warrant a therapeutic trial with aerosol therapy in all cases. Even if aerosol therapy fails to cure the abscess, the usual general improvement in the patient's condition and at least partial sterilization of the bronchopulmonary tissue will minimize the surgical risk.

Case 7 WT, a 37-year-old white male had all of his teeth extracted on the advice of his physician as a therapeutic measure for a low backache. Although penicillin was administered systemically in adequate prophylactic doses at the time of dental surgery, a few days later he developed chills and fever. There was roentgenographic evidence of dense infiltration in the left upper and right lower lobes. Systemic sulfadiazine and penicillin were administered in large doses without appreciable effect upon the clinical or roentgenographic course of the disease. There was some clearing of the infiltration in the right lower lobe, but the lesion in the left upper lobe excavated (Fig. WT 1). At this point aerosol penicillin therapy together with systemic sulfa drug administration, postural drainage and general supportive measures were instituted. After five days there was additional clearing of the lesion in the right lower lobe with noticeable diminution of the lesion in the left upper lobe. During the next five days the patient's progress clinically and roentgenographically was unchanged. The original predominantly Gram-positive flora of the sputum had disappeared completely, and there was an absolute increase in the number of Gram-negative organisms. At this point streptomycin was added to the aerosol solution. Seven days later there was remarkable improvement clinically and roentgenographically. None of the original Gram-negative or Gram-positive bacteria could be detected. During this time, however, there was a luxuriant growth of *Monilia albicans* on several occasions. Repeated diligent efforts to demonstrate acid-fast organisms by various methods failed. Aerosol iodide therapy was substituted for the antibiotic therapy. Although much decreased in number, the monilia persisted in the sputum. Systemic iodide administration and intravenous aqueous gentian violet was used as a last resort. Although the clinical signs and symptoms abated under this



CASE 7

rather heroic therapy and the roentgenogram showed marked improvement, occasional monilia could still be demonstrated on direct smear. Twelve months later there was no clinical or laboratory evidence of relapse. Instead, the roentgenogram shows sustained improvement (Fig WT 7). This patient has been engaged in his previous occupation for the past eight months and has regained his former weight and strength.

Comment The commentary on case six above is applicable to this case in its entirety. However, additionally important therapeutic observations and practices are demonstrated in this case which seemed to resist all therapeutic efforts. The development of pathogenic qualities by supposedly non-pathogenic secondary invaders was responsible for the protracted resistant illness in this case. The imperative necessity for daily examinations of the bacterial flora of the sputum, by whatever indicated bacteriologic procedure, is thus adequately demonstrated. Without this knowledge adequate and indicated therapy is difficult and invites therapeutic failures. The beneficial results of aerosol therapy in this type of case can be anticipated only if the therapeutic management is altered to parallel the constantly changing clinical and bacteriological picture.

Furthermore, in view of the fact that a lung abscess developed in this case despite the prophylactic administration of adequate amounts of penicillin systemically, reconsideration of the acceptable principles of prophylaxis is warranted. Three possible explanations for the pathogenesis of the ultimate disease should be considered in this case. In the first place, since systemic penicillin administration failed as a prophylactic measure, one is justified in questioning the efficacy and wisdom of this practice at least as regards lung abscesses. Perhaps aerosol prophylaxis is the procedure of choice in these instances. In the second place, should one consider the possibility that penicillin resistant microorganisms were either present or developed following the prophylactic use of this agent? Finally, was the pulmonary anatomy in this particular case previously altered by some antecedent disease process so as to preclude the anticipated effectiveness of prophylactic systemic penicillin administration? These possibilities although based on the presumptive observations of one case, nevertheless, are worthy of serious consideration and investigation. Until a satisfactory answer is forthcoming, aerosol antibiotic prophylaxis with, or without, systemic antibiotic administration is certainly worthy of empirical trial.

Conclusion In addition to the cases reported above, the author has observed the beneficial effects of aerosol therapy in a large number and variety of other common acute and chronic bronchopulmonary disorders. Palliative effects of this form of therapy

were uniformly striking in bronchial asthma and emphysema. Similar improvement was noticed in one case of polycystic lung disease and in one case of Ayerza's disease. In several cases of infectious asthma aerosol antibiotic therapy produced lasting remissions as well as palliative results. Aerosol antibiotic therapy is extremely valuable as a palliative and prophylactic measure in the preparation of patients for pulmonary surgery and bronchoscopy. Not infrequently, the preoperative aerosol preparation of patients for major pulmonary surgery results in unanticipated permanent cures. The use of aerosol therapy prophylactically and therapeutically is indicated in all bronchopulmonary disorders which do not respond to the systemic administration of antibiotics and other agents.

Some investigators have reported adequate and even more effective therapeutic antibiotic blood levels following aerosol administration.^{3,10} This method of antibiotic administration is, nevertheless, not recommended as a form of systemic therapy since absorption from the pulmonary tissue is influenced by too many unpredictable and variable factors.^{3,10} Therefore, it is felt that aerosol therapy should be reserved exclusively for those cases in which systemic antibiotic administration fails or is not expected to achieve the desired therapeutic results.

SUMMARY

1) A simple method for the administration of antibiotic and other indicated aerosol therapy in the treatment of acute and chronic bronchopulmonary disorders has been presented.

2) The results achieved and problems encountered in a representative group of patients suffering from common varieties of ordinarily resistant, acute and chronic, bronchopulmonary disorders treated with aerosol therapy have been recorded.

3) The importance of palliative, prophylactic and therapeutic aerosol administration in the medical and surgical management of bronchopulmonary diseases has been adequately demonstrated.

RESUMEN

1) Se presenta un método sencillo para la administración de antibióticos y otros medicamentos indicados por la vía del aerosol.

2) Se refieren los resultados obtenidos y los problemas que se encuentran en un grupo representativo de las diferentes variedades de enfermedades broncopulmonares ordinariamente resistentes, usando el aerosol.

3) La importancia del aerosol usado como paliativo, preventivo y terapéutico en el dominio de los padecimientos de orden médico o quirúrgico, ha sido demostrado adecuadamente.

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D I S C U S S I O N

DAVID WATERMAN, MD, FCCP

Knoxville, Tennessee

The administration of aerosol antibiotics and other drugs can be a simple thing and we have found that the use of the same apparatus Dr Friedman has mentioned has been most satisfactory, and that more complicated methods are unnecessary

Any chest man has patients referred to him who have had chronic cough for years, have been treated by all the usual expectorants, and gallons of cough syrup, intramuscular penicillin, sometimes inadequate aerosol penicillin and have had no relief We became interested, particularly in the chronic bronchitis group, three or four years ago and purely experimentally, started what we felt was a fairly well controlled clinical study as to what could be done

For bronchiectatics we have been using bronchoscopy and penicillin by aerosol or intramuscularly in preparation for surgery and in palliation for a long time We have studied about 340 patients with chronic bronchitis

We treated a group with bronchoscopy alone, with definite benefit From a group treated with aerosol alone and also a group with

bronchoscopy and aerosol Recently we have been studying a group with bronchoscopy and penicillin dust but are not as well satisfied with that as we are with aerosol

There is advantages in bronchoscoping a good number of this group as mechanical aid following bronchoscopy After cleaning out the bronchial tree, aerosol treatment is started

The second advantage of bronchoscopy is in diagnosis We have picked up five carcinomas of the lung on bronchoscopy either on direct or indirect signs or through the study of the secretions later for tumor cells that were previously unsuspected We also see the reaction of the bronchial tree and from which branches the secretion is coming

Aerosol is not a substitute for surgical therapy We occasionally get brilliant results from aerosol and it deserves its place but the majority of them will have to be treated as we have treated them in the past We have the clinical impression that this regime has benefited the bronchitis group much more than anything we have ever done

Our regime is as follows After the patient has bronchoscopy, he is started on aerosol penicillin five times a day, 25,000 units every three hours At the same time we give expectorants and postural drainage routine even though the patient may not have a great deal of sputum We get five different studies on the sputum, first a smear for spirochetes and other organisms, second, a culture for identification of organisms, third, a tuberculosis concentration culture, fourth, a fungus culture, and fifth, we make an autogenous vaccine which seems to work better when made from bronchial secretions than from expectorated sputum and is certainly more efficacious than stock vaccines This group of patients have permanent pulmonary damage and we are not going to give them a new set of lungs, all we are doing is controlling the infectious factor, but if we can do that, many of them are able to live relatively normal lives We invariably take these patients off smoking and I dont believe there is any single part of the treatment that is more important as far as prolonging the benefit is concerned

A WORTH HOBBY, M D, F C C P
Atlanta, Georgia

We have been using aerosol with air and the results are as good as with oxygen

Some believe the concentration of the solutions of antispasmodics is rather high Dr Friedman is correct in his use of that

concentration Antispasmodics in aerosol are only about 50 per cent absorbed

I have been using Iodolac as an inhalation for some time but it is a little too weak Aeorsol itself has proved beneficial but I believe we may shorten treatment by using aerosol and intramuscular administration at the same time I want to commend search for acid-fast bacilli in every coughing patient before the administration of any kind of treatment It is surprising in how many of them we find acid-fast bacilli with an entirely negative x-ray film Whether the acid-fast bacilli are tubercle bacilli or not is our problem

M JAY FLIPSE, M D , F C C P

Miami, Florida

Aerosol may be of benefit in long continued asthma that has had no relief from other measures of therapy In some instances, this type of therapy will give spectacular response, particularly if the aerosol is combined with $\frac{1}{4}$ cc of 1 per cent aqueous synephrin As a rule, we do not find it necessary to use large doses, 25,000 units per cc in normal saline given three or four times a day, either alone or in combination with intramuscular penicillin

Closing Remarks

Louis L. Friedman, M D , F C C P , Birmingham, Alabama From my original remarks and those of the various discussants, it is apparent that we are only beginning to understand and realize the multiple applications of aerosol therapy Opinion regarding the correct therapeutic application of aerosol antibiotic therapy is divided I do not share Dr. Hobby's feeling regarding the use of simultaneous parenteral therapy except in a few instances As a rule, those cases which are suitable for aerosol therapy have already had a trial with systemic therapy One of the chief indications for aerosol antibiotic therapy is the failure of treatment by the oral or parenteral routes Additionally, in the treatment of bronchiectasis, it is well to stress the fact that aerosol therapy is no substitute for surgical treatment It should be considered as a palliative procedure, and a preparatory measure for surgery only Likewise, in lung abscesses which do not respond to a fair trial with aerosol therapy, the internist should not hesitate to recommend surgical intervention

When aerosol therapy is used in treatment of bronchopulmonary

disorders, it is important to study the bacterial flora of the secretions regularly and to make the necessary adjustments in the antibiotic therapy as indicated. The number of agents which can be used as aerosols is practically limitless and depends only upon their ability to enter into a satisfactory solution for nebulization.

I have recently used aerosol antihistaminic therapy in the treatment of bronchial asthma. Benadryl, injectable, as dispensed by Parke, Davis and Company is a satisfactory drug for this purpose. Ten milligrams (1 cc) of this solution is the usual dose. However, the amount used in each patient and in each treatment depends upon the individual response. When the indication exists, one may administer combined aerosol antihistaminic — sympathomimetic mixtures. A more detailed report of the work with aerosol Benadryl will appear in an early issue of the *Southern Medical Journal*. The drug acts as a bronchodilator and expectorant agent. We have used it in combination with antibiotics in the treatment of bronchopulmonary infections with noticeable benefit. In more than 200 cases observed and studied to date we have not observed any local or systemic allergic response to penicillin or any other antibiotic when benadryl has been included in the aerosol solution.

Treatment of Tuberculosis with Promizole A Clinical Investigation with Matched Controls

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Beginning in 1940, it appeared likely that derivatives of diamino-diphenylsulfones, such as promun offered new hope for the development of specific antibacterial agents against this most common of chronic infectious diseases of the human race. Very quickly chemists instituted a program to develop synthetic drugs of increasing efficacy and decreasing toxicity. The compound named "4, 2'-diaminophenyl-5'-thiazolesulfone" (promizole) was subjected to extensive experimental studies at the Institute of Experimental Medicine, Mayo Foundation and was shown to be a moderately effective drug of low toxicity for animals. Preliminary clinical studies at the Mayo Clinic and Mineral Springs Sanatorium demonstrated that it was a drug of low toxicity to human beings but that its therapeutic efficacy was not demonstrable to a degree adequate to permit recommending the drug. Therefore a controlled clinical study appeared necessary.

In carrying out this study our group had three objectives:

(1) To explore the possibilities of evolving a technic of clinical study to evaluate therapeutic agents in a protean disease such as tuberculosis. (2) To determine if promizole exerts a recognizable antibacterial effect in certain clearly definable types of pulmonary tuberculosis. (3) To make available to the inmates of mental hospitals of Minnesota any therapeutic benefits possible. These unfortunate persons have access to little or no direct therapeutic measures such as collapse treatment and surgery and are often unable to cooperate with bed rest treatment.

This project was instituted in the autumn of 1943. At that time there was a population of approximately 14,000 inmates in the hospitals for the mentally ill of Minnesota. Of this group there were over 2,000 who showed some evidence of reinfection type tuberculosis by x-ray. More than 1350 films extending through

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The Promizole used in this study was furnished through the courtesy of Parke, Davis and Company, Detroit, Michigan

several years of observation were available on patients in nine mental hospitals with facilities to cooperate in the study

Patients were selected for inclusion in this study on the basis of x-ray findings primarily. All patients whose disease had tended to improve spontaneously were excluded and those patients whose disease was of chronic nature were excluded. We felt it necessary to prove by serial films that the disease process was unstable and progressive and that there was a substantial component of exudative bronchopneumonic tuberculosis of apparently reversible type before a patient could be included in this investigation. After a patient had been selected for this study it was then necessary to pair him with another patient of about the same age whose disease was of similar quality, extent and distribution and to secure unanimous agreement of the investigators that the outlook of each one of the pair was apparently the same. Needless to say, many highly interesting and otherwise suitable cases were excluded because it was not possible to find a comparable patient to pair with the candidate for treatment. When a pair of patients had thus been matched to the approval of the group, a coin was tossed to determine which of the two patients would receive treatment with promizole and which would be given a placebo treatment consisting of Brewer's yeast tablets.

Adequate clinical records were maintained and films on each patient taken at monthly intervals. A number of patients selected for treatment were excluded due to their inability to cooperate because of their psychiatric condition. Oral medication was often refused. Others were excluded because of toxic reactions which did not permit treatment in adequate dosage for sufficiently long periods of time.

Evaluation of Results

Results were evaluated on the basis of roentgenographic improvement alone. Films were reviewed without the observer having knowledge as to whether the patients belonged in the treated or in the control group. Because of the type of disease in the cases selected the progression was usually so obvious and death so frequently occurred during the period of study that no particular difficulty was encountered in evaluation.

Results Obtained

The following table shows the status of the project when it was concluded in December 1944. It will be noted that only 24 pairs (48 patients) finally qualified for inclusion in this table. Reference to the last column will show that two-thirds of all patients were either dead or worse by that time and that only 15 per cent

had shown improvement, which was usually of only slight degree. It will also be noted that there is little detectable difference between patients in the treated series and those in the control series.

Treatment of Pulmonary Tuberculosis with Promizole (December 1944)

	Controls	Patients Treated	Total Patients	Per cent
Died early (within 30 days)	5	3	8	66
Died later	4	4	8	
Worse	8	8	16	
No change	6	3	9	19
Slight improvement	1	4	5	15
Moderate improvement	0	1	1	
Marked improvement	0	1	1	
TOTAL PATIENTS	24	24	48	

SUMMARY

Evidence developed by his study indicated that the severe progressive, potentially fatal type of bronchopneumonic tuberculosis selected for treatment with promizole did not respond to such medication given under the conditions of this experiment.

It is quite possible that the handicaps imposed were too severe to be overcome. It is also possible that patients with associated mental disease are less likely to respond favorably to therapy than individuals with normal mentality.

Subsequent experience with streptomycin has demonstrated to the satisfaction of this group of investigators that a large percentage of the patients selected for this study would have made at least temporary improvement with streptomycin therapy had this drug been available at that time.

Tuberculosis and Antihistaminics*

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I General and Pharmacologic Considerations

Synthetic antihistaminic substances, first discovered in 1933 by Fourneau and Bovet¹ while seeking a means of combatting the physiologic effects of histamine, have now been used in a large number of fields. The indications have been extended beyond the point of sound pharmacologic judgement and to this day reports are being published which are nothing short of fantastic.

Their mode of action, from the antianaphylactic standpoint, is based on the histamine theory of sensitivity (Lewis²) related in large measure to anaphylaxis, allergy, and to histamine poisoning. There is little doubt that histamine is an important factor in anaphylaxis in animals as in human allergy. In an individual in contact with an antigen to which he has been sensitized, a reaction occurs between antigen and its specific antibody which, liberating histamine or a substance analogous to histamine, provokes anaphylactic shock. Histamine is furthermore a chemical substance present under normal conditions in tissue and it has been shown by Katz³ that all allergic reactions provoke its liberation. In addition the various antihistaminic products react in such a fashion in anaphylactic conditions as to leave little doubt of the role played by histamine in accidents of this type. The still imperfect techniques which are used to measure blood histamine today in patients with allergic conditions do not allow confirmation, although the similarity of results in certain clinical conditions as well as in laboratories are certainly in favor of this hypothesis.

The activity of these antihistaminic substances is demonstrated in certain cases accompanying conditions of capillary permeability of which urticaria, angioneurotic edema, vasomotor rhinitis are examples while in other clinical conditions such as asthma or dermatitis, their indications remain restricted to cases where the allergic origin of the phenomena can be proved readily. In still other clinical states particularly in the area of the nervous system they do not act by virtue of their antihistaminic property but

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rather by those pharmacologic attributes which are apparent in other synthetic substances

There are three general types of antihistaminic agents which have been recognized and listed by Bovet ⁴

1) Those products with selective properties related to histamine itself through the mediation of histaminergic substances of the pyridine group

a) derived from aminopyridine neo-antergan, pyribenzamine, histadyl, chlorothene,

b) derived from pyrimidine neo-hetramine

2) Those products which because they are analagous in structure and pharmacologic action are related to sympathetic poisons, and are either sympathicolytic or sympathicomimetic

a) Phenol ethers 929 F,

b) derived from the aniline group 1571 F, antergan, diatrine,

c) derived from the imidazoline group antistine,

d) derived from the tetrahydropyridendene group theophorine

3) Those products which are antagonistic to acetylcholine with antihistaminic action and severe spasmolytic properties

a) Benzyl ethers and its derivatives benadryl, decaprime, histaphene, antadryl,

b) derived from the phenothiazine group phenergan (RP3277), amydril, pyrrolozole,

c) diphenylaminopropane and derivatives aspasan, trimetone

All of these products have varying degrees of toxicity and in many instances are poorly tolerated in humans. The antianaphylactic power of these compounds as well as their action on the Schultz-Dale phenomenon does not parallel their antihistaminic action. Furthermore they all present certain pharmacologic properties which although varying in considerable degree may be summarized as follows

a) They prevent the spasm of the smooth muscle of the uterus, intestine, and bronchi produced by histamine, through a reaction comparable to atropine but to a considerably less degree

b) They prevent contraction and relaxation of blood vessels and by this means prevent increased capillary permeability

c) They have a local anaesthetic action. This prevention of cutaneous reaction to histamine whether provoked by irritants or allergens can not be attributed to an antihistaminic effect if this local anaesthetic action can not be eliminated by other appropriate means (Loew⁵)

It is readily seen that these substances do not have a strict specificity, but this point is not really appreciated. On the other hand there is as yet no unanimity of opinion regarding the mechanism of antianaphylactic action

II *Tuberculous Allergy*

In view of the efficiency of these different compounds in certain allergic conditions, it was but a short step to attempt their use in tuberculosis. It should be noted that the word allergy, introduced in 1908 by von Pirquet and used in the sense of "altered reaction" produced and continues to produce considerable confusion. Tuberculous allergy may be differentiated from the phenomenon of anaphylaxis on several different points as demonstrated in laboratory experiments. It is actually possible to provoke anaphylaxis to pure tuberculoprotein by injecting it into a laboratory animal free of tuberculous infection. On the other hand it is absolutely impossible to provoke an anaphylactic reaction in any animal already infected with tuberculosis and the reaction will be totally different.

In the normal animal sensitized to tuberculoprotein, an anaphylactic reaction will occur characterized by

- An immediate acute response within 15 minutes,
- No cutaneous reaction, no Arthus phenomenon (Corper⁶),
- The reaction may be passively transferred,
- The reaction may be transferred to lineal descendants

This reaction then is a humoral response due to circulating antibodies in blood and body fluids producing an immediate response.

In the animal infected previously with tuberculosis there will be an allergy characterized by

- No acute intoxication, requiring hours to produce a fatal reaction and appearing only after one, six or 24 hours,
- A definite positive cutaneous reaction,
- The allergic state is not passively transferred,
- The allergic state is not an inherited characteristic

In the latter situation this is more of a tissue response, the antibodies present being fixed to the cell structure producing a delayed reaction. There are obviously two dissimilar reactions in tuberculosis. While the anaphylactic type of sensitization can be established through the injection of pure tuberculoprotein in a virgin organism, this same substance is a chemically extracted toxic material and does not produce the same reaction as the tubercle bacillus *in vivo*. The special allergic type of sensitization can be established only in an organism previously exposed to a bacillary infection and must be considered as a type of bacillary sensitization.

Certain investigators seem to consider these reactions as similar and believe that there is a common principle basic in these phenomena. It is felt that the different forms of sensitivity are effects resulting from the interreaction of antigen and antibody under

different physiopathologic conditions but probably liberating a homologous toxic substance. It is possible but not proved and up to this time not demonstrated that in the tuberculin reaction there is actually a liberation of histamine. If antihistaminic agents can have any effect in clinical tuberculosis it must be therefore by some other mechanism.

From what has already been presented it seems impossible at this time to say that there is a type of tissue or cell other than involuntary muscle or vascular endothelium which can be directly sensitized to an antigen-antibody reaction. This must be similar in all respects to those produced by direct action of histamine or a similar substance on the same organs in an anaphylactic reaction (Dale and Laidlow,⁷ and Rich⁸). In tuberculosis, a type of bacillary sensitivity can exist in the total absence of all anaphylactic sensitivity to tuberculin. That is why one may say that in bacillary sensitization, involuntary muscle as well as vascular endothelium are not sensitized, a fact well proved in vitro and in vivo and that the antibody is bound up intimately in the individual cells. Therefore any tissue which does not have a good capillary bed can be sensitized to the action of the specific antigen in the bacillary type of sensitization but will not respond to the action of antihistaminics. On the other hand anaphylactic phenomena are produced only in tissues where a larger blood supply is present and will respond to the administration of antihistaminic substances. This may explain why in bacillary sensitization the circulating antigen in the blood can induce an inflammatory process, necrosis, or hemorrhage in any area of the organism which is involved and the focus of infection will show a "focal reaction," a rare occurrence in anaphylaxis described, however, by Arthus and explained by him as due to the use of an impure material.

Many authors feel that under certain circumstances in clinical tuberculosis a typical anaphylactic reaction to tuberculin may occur during infection, superimposed on the bacillary type of sensitization. Corper⁹ as well as others believe that this concept is only of academic interest in tuberculous animals as well as humans and is of so little importance as not to be worthy of too lengthy discussion.

Such a situation actually may be observed under the following circumstances:

- 1) In massive dissemination
- 2) In pulmonary cortical types adjacent to pleura, a tissue extremely sensitive itself and with a large absorbable surface

A considerable depression in cutaneous sensitivity may be produced, probably due to some effect on the vascular or inflamma-

tory response of the organism rather than to autotuberculinization or tuberculin automtoxication, for the liberation of tuberculin in the body has never been proved. This latter point is of considerable clinical importance and has not been too well recognized. These types of depressed reaction especially following massive dissemination are generally of short duration, followed as a rule by a temporary increase in tuberculin sensitivity, probably due to the mobilization of large numbers of tubercle bacilli. By virtue of their action on vascular tissue, antihistaminics may have some value in this area during the acute stage (vascular blockade?). However, recent experiences of Halpern and Reber on the influence of antihistaminics on the evolution of experimental microbial infection tend to prove that such employment of antihistaminics, in paralyzing the organization of local inflammatory defenses, favor microbial dissemination. This would tend to contraindicate the use of antihistaminics in local or focal infections. Actual experimental data in animals, infected with *Salmonella typhimurium* and treated with phenergan (RP3277), showed a mortality through septicemia three times higher than that in control animals.

Can one say then that in chronic forms of tuberculosis any type of desensitization is possible through the use of antihistaminics or by any other method? Desensitization as a form of treatment has been tried and continues to be utilized by a few clinicians. Utilizing Besredka's technique of injecting patients with progressively increasing doses of tuberculin, it has been possible to give as much as 10 cc of undiluted tuberculin (Bauer¹⁰), an amount many hundreds or thousands of times that which the patient would have reacted to before sensitization. Is this however a true desensitization? It is rather an extreme tolerance because if desensitization with tuberculin produces an inhibition or alteration of sensitizing antibodies, this does not free the body of its bacilli which will resensitize the tissue as soon as treatment is discontinued and sometimes will provoke a much greater sensitivity in the immediate future. Actual tissue necrosis may occur at the site of tuberculin injection. The obvious importance of focal reactions, considered as a valuable feature in treatment in the past, need not be discussed here. If antihistaminics possess a similar desensitizing effect, should they not similarly be feared, rather than utilized?

III *The Use of Antihistaminics in Tuberculosis*

Although numerous investigators have utilized the antihistaminic compounds Rolland¹¹ with antergan, Vallery-Radot, Hamburger and Halpern¹² with phenergan, no real benefit from treat-

ment has been reported in France to date. In 1943 Boquet and Breton¹³ in their experimental trials were unable to demonstrate in guinea pigs a negative tuberculin response after prolonged subcutaneous injections of the earlier antihistaminic agents. Guy,¹⁴ was unable to obtain any effect in five patients by the use of large doses of pyribenzamine by mouth. Crip, Levine and Aaron¹⁵ could not influence the Mantoux reaction in tuberculous animals using pyribenzamine and rutin by oral route, intradermal injection, iontophoresis or the injection of a mixture of tuberculin and pyribenzamine.

The cutaneous reaction to tuberculin is obviously too variable to be considered as a precise test. It is influenced by meteorologic variations, the state of the peripheral vessels, the acquired sensitivity of the skin and many other factors. On the other hand, the antihistaminics having a local anaesthetic action may in themselves upset further the value of the test. For all these reasons the actual test result may be questioned.

The only optimistic report to date which does not accept within its framework the foregoing physiopathologic concepts, is that of Judd and Henderson¹⁶ presented before the American College of Allergists in April 1949. These investigators used benadryl, pyribenzamine, theophorine and neohetramine in the different forms of tuberculosis both pulmonary and extrapulmonary. In the latter group there were cases of lymph node involvement, larynx, and one case complicated by erythema nodosum. Doses were given of 50 mgm three times daily, increasing gradually up to a maximum of 500 mgm according to the patient's tolerance. The patients were followed by tuberculin test, x-ray, pulse, weight, appetite and other subjective symptoms. A dramatic improvement was noted in the x-rays in some patients after a short period of treatment, and it was similarly possible to demonstrate the return of the pathological lesion if treatment was stopped with return of improvement as soon as treatment was again instituted. The sputum also was decreased and the cutaneous reaction seemed less positive throughout the period of treatment. The best results were apparently obtained in the exudative lesions while the fibrocaseous responded less well paralleling the action of streptomycin.

In some cases the antihistaminics were used simultaneously with streptomycin and the authors felt sure that the results with the combined drugs were better than if they were used separately. In the discussion Wittich¹⁷ indicated that other workers had found that neohetramine was effective for the protection of animals against experimental tuberculosis in approximately half the cases although no specific action against the bacillus had been de-

monstrated in vitro We have no personal knowledge of this quoted work The hypothesis was projected that through the suppression of tuberculin sensitivity or some other product of the bacillus, the normal defenses would be better capable of combatting the infection

In view of this enthusiastic report, through the cooperation of Merck and Company, the following combination of antihistaminic drugs were tried on 30 patients with tuberculosis, neo-antergan and the new product phenergan (RP3277) described by Halpern and Ducrot¹⁸ in 1946, whose action is considerably greater than that of all known antihistaminic substances and much more prolonged This product had already been tried in France in 1947 by Vallery-Radot, Blamoutier and Halpern¹⁹ in tuberculosis without any influence on the allergic manifestations of tuberculosis or on the intradermal reaction to tuberculin

No attempt was made in this study to choose special cases for treatment and among those included were cases with far advanced lesions while others had lesions of less importance either exudative or fibrocaceous

The following dosage schedule was used Three hundred mgm of neo-antergan were given daily, divided into fractional doses through the day In addition 25 mgm of phenergan was given at bed-time because of the sedative and hypnotic effect noted in the use of this product The patients noted almost immediately that sleep was considerably better since the use of the antihistaminics

The compounds were well tolerated generally although there were occasional complaints of drowsiness, dizziness, headaches and dryness of the mouth In two instances it was necessary to discontinue medication because of vomiting, nausea, vertigo, and in one, a severe tremor

We have chosen to evaluate the treatment in our cases with the following criteria X-rays, volume of sputum, sedimentation rate, weight, and subjective complaints We have not used the skin reaction for the reasons of variability noted previously The following is a summary of the results It is to be noted that the results are given for only 28 of the 30 cases since in two cases, treatment was discontinued because of intolerance to the drug at an early date so that the treatment could not be evaluated

	X-ray	Sputum Volume	Sedimentation Rate	Weight
Slightly improved	8	5	12	14
No change	20	18	8	9
Worse		5	8	5

During the course of treatment 12 patients received streptomycin just prior to or simultaneously with the antihistaminics in a dose of one gram daily for 28 days. It should be noted that in general the most suggestive radiologic improvement occurred in this group. Another two patients who did not receive streptomycin also showed significant improvement. The first was a case of diffuse acute pleurisy complicating pneumothorax where the sputum had been negative for approximately four months, and in whom the antihistaminics quickly reduced the temperature and fluid formation in less than six days. The second patient had exudative lesions in both upper lobes which showed only slight retrogression following a course of streptomycin in March 1949. When the antihistaminics were begun, the sputum became converted in one month, the most recent x-rays showing an almost complete clearing. It should be noted that this individual was an almost perfect bed rest case during this period.

CONCLUSIONS

While a large number of our patients may be said to have shown some degree of improvement it is difficult to evaluate these findings. All of us are familiar with the psychosedative effects of any new drug in tuberculosis in which the patient goes through periods of hope and despair. The volumetric decrease in the sputum can well be due to the atropine-like effect of the antihistaminic drugs. On the other hand the excellent soporific effect of phenergan may also play a certain role. It is necessary for us to conclude then that in our limited experience the antihistaminic drugs whether alone or associated with streptomycin have not produced striking results in a trial of treatment of pulmonary tuberculosis. In this opinion we join the previous conclusions of the French investigators. An attempt will be made to choose a more select series for future investigation.

SUMMARY

1) The present knowledge of antihistaminics, particularly the pharmacologic considerations are presented.

2) Tuberculous allergy and tuberculous anaphylaxis are presented as widely different mechanisms and carefully differentiated.

3) Neo-Antergan and phenergan (RP3277) were given for several months in a series of thirty patients with tuberculosis. Although small changes in symptoms with slight improvement were noted in some cases, no definitive x-ray changes could be attributed to the use of these antihistaminics.

4) A further study using mainly cases with exudative lesions is planned.

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Antihistamines in the Treatment of the Common Cold A Preliminary Report*

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So far as we can determine only three reports on the use of antihistamine drugs in the treatment of the common cold have appeared^{1 2 4} Our interest in them in the treatment of the common cold was stimulated by the report of Brewster in 1947 on the effect of diphenylamine hydrochloride (Benadryl) in over one hundred cases Although at first we used various antihistamine drugs casually and without statistical analysis, we soon got the impression that in many patients the symptoms were modified and in a few instances the cold could be terminated within a few hours

The present study was undertaken in an effort to carefully analyze the effect of these drugs The patients were primarily medical students and student nurses on whom it was possible to maintain adequate observation and "follow-up" Because it was desired to interfere as little as possible with normal activity and work, and in order to best insure continuation of therapy, drugs known from previous experience to have few severe side effects were selected A further element in the choice of drugs was to have tablets of approximately the same size and color

Method of Study

Pyranisamine maleate (Neo Antergan†), and phenindamine (Thephorin††) were used in the study Pyranisamine was given in 50 mgm doses, phenindamine in 25 mgm doses four times daily for three days In some instances where rapid relief was obtained, patients found it unnecessary to complete a full course of therapy

At first every other, later every third, patient was given placebo tablets which were of the same shape and color as the test drugs but without medicinal effects They were given according to the same dosage schedule as the antihistamines Patients receiving these tablets were used as controls

The drugs and placebos were furnished in paper envelopes bearing only the dosage instructions and a code number No patient was informed as to the drug or placebo that was used in his case

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†Brand of pyranisamine maleate, supplied by Merck and Company

††Brand of phenindamine, supplied by Hoffmann-La Roche, Inc

The drugs and placebos were assigned in the order in which the patients presented themselves for treatment. Only those who came in complaining of a cold, with some symptoms of rhinitis i.e. nasal congestion, nasal discharge, sneezing, burning, or itching of the nasal mucosa were accepted for the study. Although it is known that in many instances the first symptom of a cold may be a sore throat, patients with this only were excluded from the report. We felt that too many other conditions may be so manifested. However, a few of the patients were given one or another of the drugs with reported benefit.

Each patient filled out a form listing symptoms and their duration, the average number of colds per year and their average duration in the past, and any allergy history. In most cases the oral temperature and the appearance of the nasal and pharyngeal mucosa were recorded. Each patient was asked to return in 48 or 72 hours for further observation. The few that did not voluntarily return in the allotted time were seen the following day through the Student Health Service. At the time of return the forms were completed. This consisted in recording the time when relief of symptoms (if any) was obtained, the duration of symptoms, the time of treatment, and a subjective comparison of the present cold with previous ones as to severity and duration. Side effects attributed to the drug were noted. The nose and throat were usually not inspected if the patient was symptom free.

No attempt was made to interpret the statements made by patients comparing the duration and severity of their present cold with previous colds, since this was based upon subjective impressions and memory.

Results

A summary of the results obtained is given in Table I. For the purposes of evaluation, patients with histories of allergy were tabulated separately. Of the total treated with antihistamines 76 per cent were benefited with partial or complete relief of symptoms, whereas only 45 per cent of the control group reported such benefit. The type of benefit afforded was primarily disappearance of, or a decrease in, nasal congestion and/or nasal discharge. Others noted relief from cough, sore throat, sneezing, etc., but we did not consider these in the benefited group unless their nasal symptoms improved also.

Eighty-eight per cent of patients with history of allergy were benefited, as compared with 72 per cent of the non-allergy group. However, this was a small group, and the apparent difference may not be of real significance. Further, it was still impossible to predict which patient with allergies might be benefited. Finally,

it is in this group that there is the greatest difficulty in differentiating an acute cold from allergic rhinitis, and the results may be subject to some question on that account

Colds were considered to be "aborted" only if symptoms were entirely relieved within 12 hours after the start of therapy and remained absent after treatment was discontinued. On this basis only seven colds could be considered as "aborted." Although a number of other patients stated that their colds were "aborted," some symptoms had persisted and therefore they were not included. Of the seven "aborted" colds, two had had symptoms for less than 12 hours, four from 12 to 24 hours, and one for a longer period.

Since we felt that it was extremely difficult, if not impossible, to determine the presence of a cold in patients whose symptoms were of less than three hours' duration, treatment was not given where symptoms had been present for a lesser period. At the other extreme, was the group who had had symptoms for more than 24 hours, in only a few of these were symptoms present for more than 48 hours. Two cases in this group were excluded from the tabulation because it was not possible to determine whether the clearing of symptoms was due to the effect of the drug or to the natural course of the cold. All other cases treated are included in this report.

There was no definite correlation between duration of symptoms prior to therapy and effectiveness of therapy, either as to relief of symptoms or number of colds aborted. A greater percentage with symptoms of 12 to 24 hours' duration were relieved than either of the other groups, but here again this series was small, and statistical significance may be lacking. Further breakdown of the small group (20) whose symptoms had been present less than 12 hours likewise showed no correlation between results of treatment and duration of symptoms.

TABLE II
Side Effects

	Drowsiness	Insomnia	Nervousness	Vertigo	Weakness	Headache	Dry Mouth	Total Cases with Side Effects	Per cent of Cases Treated
Pyranisamine maleate	6	1		2		1	4	13*	39
Phenindamine	1	4			1		1	7	26
Controls	1		1	1				3	10

* More than one side effect reported by one patient

The principal side effects reported for each drug are recorded in Table II. Only one patient complained of more than one side effect. It is of interest to note that one patient receiving a placebo complained of numbness and tingling in the hands. For the most part the side effects were not severe, and in no instance was a drug discontinued because of them.

Discussion

The results reported here show a much smaller percentage of patients benefited than in the series reported by Brewster,² or Gordon.⁴ Although treatment was not initiated in any case with symptoms for less than three hours, we did not observe any definite correlation between duration of symptoms and benefits obtained, including "aborted colds." Patients with a history of allergy of some type were benefited in a higher percentage than the others.

There was no significant difference between results from pyranisamine maleate and phenindamine. Although the former gave a higher percentage of side effects, none was severe enough to interfere with therapy. Results in the control group, although small in number, were similar to those obtained in other investigations of the common cold, particularly efforts to prevent colds, such as those of Cowan, Diehl and Baker.³

Although our results are not startling, it appears that there was a definite and significant difference in the percentage of cases benefited with antihistamine therapy, as compared to the control group. While no attempt at analysis was made, it may be that those cases that fail to benefit, or those that have a recurrence of symptoms after therapy is stopped, should be re-evaluated, particularly with reference to possibility of infection of the paranasal sinuses.

We do not claim, as a result of this investigation, that there is an altered response to viral or bacterial infection, but rather that there may be a modification of symptoms. A possible rationale for the use of the antihistamines in the manner here reported is suggested by the report of Troescher-Elam⁵ and co-workers, who noted the presence of a histamine-like substance in nasal secretions from patients with the common cold, in quantities at least equal to that from patients with allergic rhinitis.

SUMMARY AND CONCLUSIONS

- 1) Sixty-three cases of the common cold were treated with antihistamines and 29 with placebos as a control.
- 2) There appeared to be a definite and significant percentage of cases benefited by the antihistamines.

- 3) Few colds seemed to be truly "aborted" by this therapy
- 4) Neither duration of symptoms of a cold nor a history of allergy is any indication of the amount of benefit that may be expected
- 5) The results obtained in this small series warrant further critical investigation and study

SUMARIO Y CONCLUSIONES

- 1) Sesenta y tres casos de catarro comun fueron tratados con antihistaminas y 29 con "placebos" como testigos
- 2) Parece que hay un porcentaje definido y significativo de casos beneficiados por los antihistaminicos
- 3) Pocos catarros parecen haber sido verdaderamente "abortados" por esta terapéutica
- 4) Ni la duración de los síntomas, ni los antecedentes de alergia en un caso de catarro comun, son indicadores del grado de beneficio que es de esperarse
- 5) Los resultados obtenidos en esta pequeña serie autorizan a una investigación ulterior y estudio crítico

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The Effects of Administration of Protein Hydrolysate (Amigen), Testosterone and Folic Acid on Nitrogen Balance in Patients with Chronic Pulmonary Tuberculosis*

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Although extensive work¹⁻⁸ has been done on the nutritive value of intravenous alimentation with amino acids for relatively short periods of time in acute medical and surgical problems, little, however, has been reported in chronic disease states. Elman and Wiener⁹ were among the first to extensively study in patients the intravenous use of amino acids. They found amino acid therapy of value in malnutrition and in the prevention of post-operative starvation. Confirmation of the beneficial effects of parenteral use of amino acids has been reported by other investigators.¹⁰⁻¹² Farr,¹³ in studies on nephrotic children, reported that positive nitrogen balance may be obtained with the injection of enzymatic hydrolysates providing about 5 per cent of the total nitrogen intake.

The purpose of the present study was to investigate alterations in nitrogen storage following administration of protein hydrolysates in patients with a chronic wasting disease such as pulmonary tuberculosis or ulcerative colitis. In addition, it seemed desirable to determine the efficacy of testosterone and folic acid as dietary supplements in promoting nitrogen retention.

Materials and Methods

Five patients with chronic pulmonary tuberculosis and one with chronic ulcerative colitis were intensively studied to ascertain the effect of intravenous administration of protein hydrolysates. Three of the 5 tuberculous patients were in good nutritional state and in nitrogen equilibrium, the other two, as well as the patient with ulcerative colitis, were in poor nutritional state in negative nitrogen balance.

The patients selected were hospitalized for many months to provide a base-line period. The weight and general condition of

*From the Pulmonary and Medical Divisions of Montefiore Hospital. This work was made possible by a generous grant from Mead Johnson and Company.

each patient were closely followed throughout the experiment, and laboratory studies were reported at frequent intervals. The observation periods varied from four to 18 months and included successive cycles of control and therapy periods.

The source of amino acids used in this investigation was Amigen,^{*19} a hydrolysate of casein made by enzymatic digestion of pork pancreas. The periods of Amigen administration were from one to eight weeks and the dose was 1,000 cc or 2,000 cc of 5 per cent Amigen. Finally, periods of testosterone^{**} and folic acid^{***} therapy with or without Amigen were studied for comparison. Daily intramuscular injections of 25 mgms of testosterone and 10 mgms of folic acid for five days for each week were employed.

These patients were under the direction of a specially trained graduate nurse during the period of study. A dietician was in charge of the kitchen where the food was accurately weighed and the menus planned to the palate of each patient. The daily caloric and nitrogen intake was computed from Sherman's²⁰ Tables with allowances made for uneaten food which was carefully weighed.

All urine and stool specimens were collected throughout the 24 hour period. Total 24 hour urinary outputs were preserved with toluene and pooled for a six day period. The daily urine specimens were analyzed for creatinine²¹ as a check on the adequacy of the collection of the specimens. Urine specimens in which the creatinine figures were too low were discarded as inadequately collected and were not pooled. The total urinary nitrogen output was determined from the pooled specimens by the gasometric micro-Kjeldahl method²² and computed on a 24 hour basis.

The stools were collected daily, preserved with 500 cc of 10 per cent sulfuric acid and pooled for a six day period. The pooled specimens were weighed and homogenized by vigorous stirring for one hour with an electric mixer. A weighed sample of 10 to 15 gms was then dissolved by heating with concentrated sulfuric acid, cooled and made up to a known volume. A suitable amount was sampled for analysis and the nitrogen determined as for the urine.

Nitrogen balances were calculated from the data tabulated for the total nitrogen intake and total nitrogen excretion.

Plasma volume studies were made using the dye T 1824.²³ The serum proteins as well as their fractions (including the three globulin groups) were chemically determined.²⁴ The total circulating plasma protein was then calculated from these data.

*Amigen for this experiment was liberally supplied by Mead Johnson and Company

**Testosterone propionate was furnished through the courtesy of the Ciba Company

***Folic Acid was supplied as "Folvite" by the Lederle Laboratories

Results

The experiment was divided into control and experimental periods. The first control period of two to five weeks was followed by a period of intravenous administration of Amigen for two to six weeks. Similar successive control and treatment cycles followed. During these alternating phases the amount and length of periods of Amigen treatment varied. The daily dose of Amigen was usually 1,000 cc given five days a week, but at other periods 2,000 cc were employed. Periods of Amigen combined with testosterone and folic acid followed the periods of Amigen therapy alone, and lastly periods of testosterone and folic acid without Amigen were studied for comparison.

Patient No 1 (H W) M H No 40749 This 44 year old white male complained of fatigue and weight loss of 25 lbs in August 1943. He was admitted to Montefiore Hospital on May 19, 1944, where a diagnosis of bilateral fibrocaseous tuberculosis was made. The sputum was positive for tubercle bacilli but was negative after February 5, 1945. Radiographic examination revealed numerous nodular densities throughout the upper one-third of the left lung. The right upper lobe was obscured by a density which was sharply delimited by the horizontal fissure and there were several nodular densities scattered throughout the right mid-lung field. On bedrest he gained 16 lbs and on semi-ambulant care he continued to gain an additional 24 lbs. His nutritional state was good when he came to the metabolic wards for treatment with Amigen. During treatment for one year, he gained another 5 lbs. On discharge from the hospital, his x-ray films revealed clearing of the previous infiltrations.

The findings on this patient (No 1) during the control and experimental periods are shown in Chart 1. From these it appears that during periods one to 10 no marked nitrogen retention was obtained. In periods 21 to 64 the mean nitrogen balance varied from plus 5 to plus 11 gms in 24 hours. The explanation for this observation may be found in the influence of ambulation on nitrogen balance.²⁵ In the beginning of the experiment the patient was confined to bed during the period of Amigen administration but was allowed to be ambulatory during the control period. In the latter part of the experiment the patient was ambulant during the Amigen as well as during the control period. Nitrogen balance increased in this patient when testosterone was given with Amigen, but this response was not as marked as in other patients. Folic acid with testosterone produced a positive nitrogen balance during the one period in which it was studied.

A tendency for the total circulating protein and body weight to rise during Amigen administration when the patient was in positive balance and to fall again during the control periods was observed. The rise in total circulating protein was probably partly

due to an increase in plasma volume as well as in plasma protein concentration

Patient No 2 (NR) MH No 39256 The onset of illness in this 35 year old white male occurred in 1935 The sputum was positive for tubercle bacilli and x-ray examination revealed tuberculosis of the right lung After induction of artificial pneumothorax, the sputum became negative In 1943 he had several small hemoptyses and was admitted to Montefiore Hospital His sputum again became positive for tubercle bacilli X-ray films at this time showed the right lung to be fibrotic with a thickened

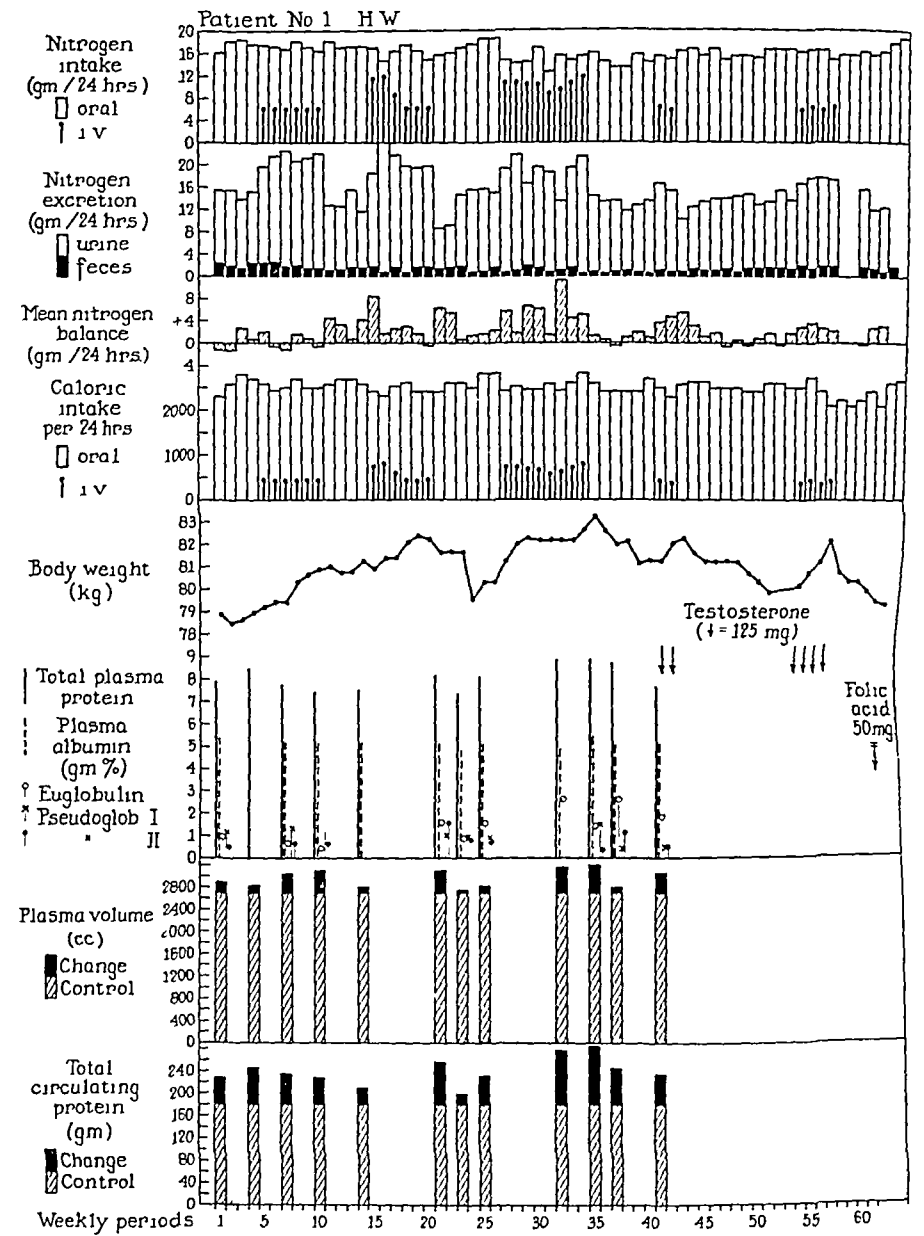


CHART 1

pleura The left lung had numerous infiltrations in the upper portion with at least two large cavities He was transferred to the metabolic ward for treatment with Amigen However, his disease progressed steadily and he expired on September 27, 1945

The observation periods on this patient (No 2) were short as illustrated in Chart 2 The first reliable laboratory studies available are for the period of Amigen administration when the nitrogen balance was plus 4.24 gms per 24 hours During the six week control period the nitrogen balance fell to plus 1.23 gms During both the Amigen and control periods the patient was confined to bed Because this patient was studied for a relatively short period, no conclusions could be drawn as to the effect of therapy

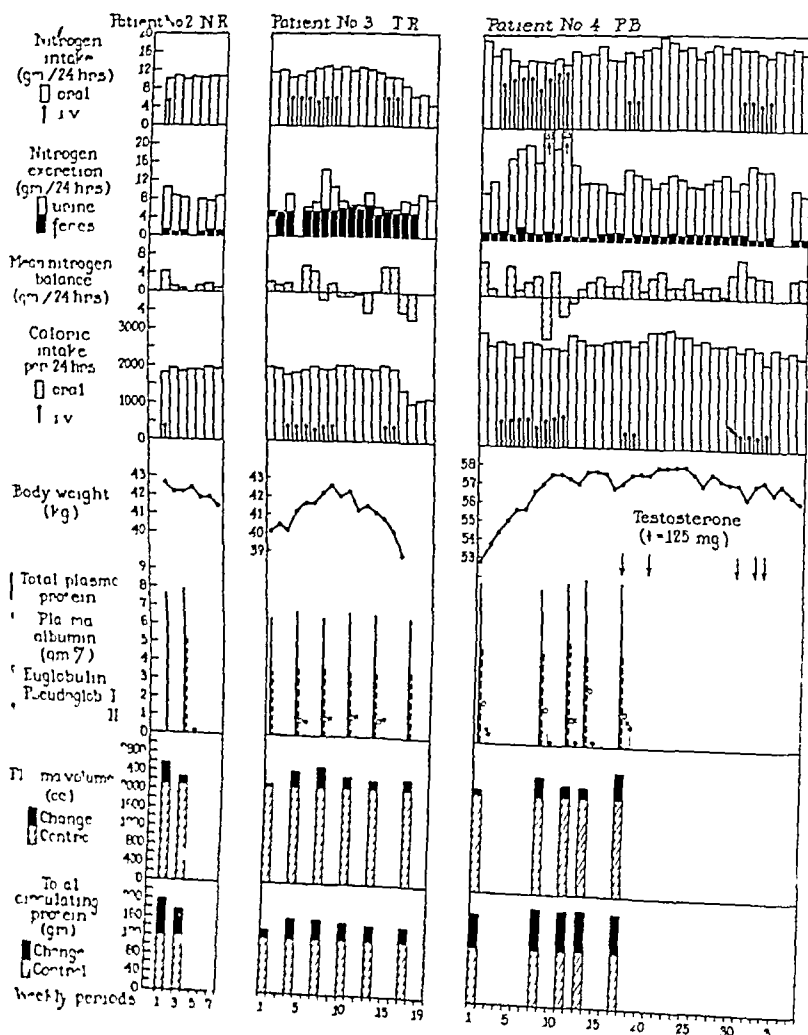


CHART 2

Patient No 3 (T R) M H No 37448 After several admissions to other hospitals because of diarrhea, a 17 year old white male entered Montefiore Hospital on September 17, 1943 with the complaint of diarrhea and fever. A diagnosis of non-specific colitis was made. Under intravenous Amigen therapy, the patient gained 30 lbs in three months. He was discharged but readmitted shortly thereafter in November 1944 with an exacerbation of symptoms. On admission the dietary regimen was carefully supervised and large doses of Amigen were given. The patient developed persistent watery stools, became moribund and died on July 31, 1945.

When this patient was observed for a preliminary two week period, the nitrogen balance was found to be plus 1.85 gms per 24 hours. For the next six weeks Amigen was given with a consequent rise of positive nitrogen balance to 2.51 gms per 24 hours, but during the control period which followed, the nitrogen balance fell to minus 1.31 gms per 24 hours. When the Amigen was resumed, the positive nitrogen balance again rose to plus 5.69 gms per 24 hours but changed to a negative balance, minus 5.02 gms per 24 hours, when discontinued. During the experiment, the patient remained in bed.

The patient lost large amounts of nitrogen in his stool because of diarrhea. During the periods of Amigen administration, nitrogen excreted in the stools remained unchanged while the nitrogen excreted in the urine increased, but was less than the amount of nitrogen intake with a consequent result that the nitrogen balance increased.

The data on patient (No 3) presented in Chart 2 revealed that the nitrogen retention was more marked when Amigen was administered after a period of negative balance than when it was given following an initial period of a positive nitrogen balance. The body weight rose from 40.1 kg to 42.6 kg during the 6 week Amigen period. The plasma volume rose from 2,100 cc to 2,500 cc and the total circulating protein rose from 137 to 162 gms during the same period, while the concentration of total proteins remained unchanged.

Patient No 4 (P B) M H No 40646 A white male aged 25 years rejected for military service in October 1942 because of pulmonary tuberculosis was admitted to Montefiore Hospital on April 3, 1945. In December 1944 his sputum was positive for tubercle bacilli and x-ray examination revealed extensive bilateral pulmonary disease with cavitation in both upper lobes. Bilateral artificial pneumothorax was attempted and abandoned after a brief period because it was technically ineffective. Clinically and radiographically there was evidence of progression of his disease and he left the hospital against advice.

During the first week of a control period, patient (No 4) was ambulatory, and the nitrogen retention was plus 4.4 gms per day.

(Chart 2) In the following eight weeks 2,000 cc of Amigen were given daily and the patient remained in bed most of the day. During this period, the nitrogen retention balance remained unchanged. Amigen combined with testosterone was given for two weeks following a second control period, a marked rise in the nitrogen retention to plus 6.02 gms per day was noted but fell to plus 1.71 gms per day during the first week of the following control period.

On testosterone alone, for a period of one week following this control period, the nitrogen retention again reached plus 4.44 gms per day and remained so for the next four weeks. For this latter four week period, the patient was on diet alone and his nitrogen balance was plus 3.7. Part of the positive nitrogen balance was probably a carry-over effect from the testosterone therapy.

A five week control period, following one week intermission, revealed that the nitrogen retention fell to plus 2.53 gms per day. Amigen with testosterone was administered for a two week period and the nitrogen retention rose to 7.02 gms per day. When Amigen alone was again given for a two week period, the nitrogen retention fell to plus 4.81 gms per day. The caloric intake also dropped off in the second week. After a four week control period the nitrogen retention still remained at 4.64 gms per day.

This patient showed an increase in plasma volume of 12 per cent and in total circulating protein of 10 per cent following eight weeks of double dose Amigen administration. The body weight rose from 54.4 kgs to 58 kgs during the same period. Graphic representation of the study on this patient is given in Chart 2.

Patient No 5 (PH) MH No 48496 A 26 year old white male was hospitalized in 1933 because of severe hemoptysis. Sputum was found to be positive for tubercle bacilli and fibrocaceous tuberculous involvement was demonstrated by x-ray film in the left lung. Artificial pneumothorax was attempted but discontinued because of obliterative pleuritis. Several small hemoptyses occurred and a contralateral lung lesion appeared. Pneumothorax was also attempted on this side and was abandoned because of the development of pleural effusion. A three stage thoracoplasty on the right side was completed in May 1943.

His sputum remained positive for tubercle bacilli and the lesion in the left lung was steadily progressive in spite of strict bedrest during the entire hospital stay. During the time he was receiving Amigen, he had elevations in temperature and a cough which induced vomiting. Serial roentgenograms revealed slow, steady progression of his disease with bilateral cavitations. He died December 15, 1946.

From Chart 3, patient No 5, it can be seen that during the initial four week control period, this patient showed a negative nitrogen balance in spite of adequate caloric and nitrogen intake. Administration of 1,000 cc of Amigen daily for six weeks resulted in nitro-

gen equilibrium This was maintained during the subsequent five weeks on diet alone Amigen given for four weeks further increased nitrogen retention to plus 15 gms per day During the following three weeks, when the patient received diet alone, the nitrogen balance remained at plus 1 47 A long Amigen period of eight weeks followed during which the nitrogen balance fell to equilibrium The oral caloric intake dropped and the patient was intermittently febrile and had a cough associated with vomiting during

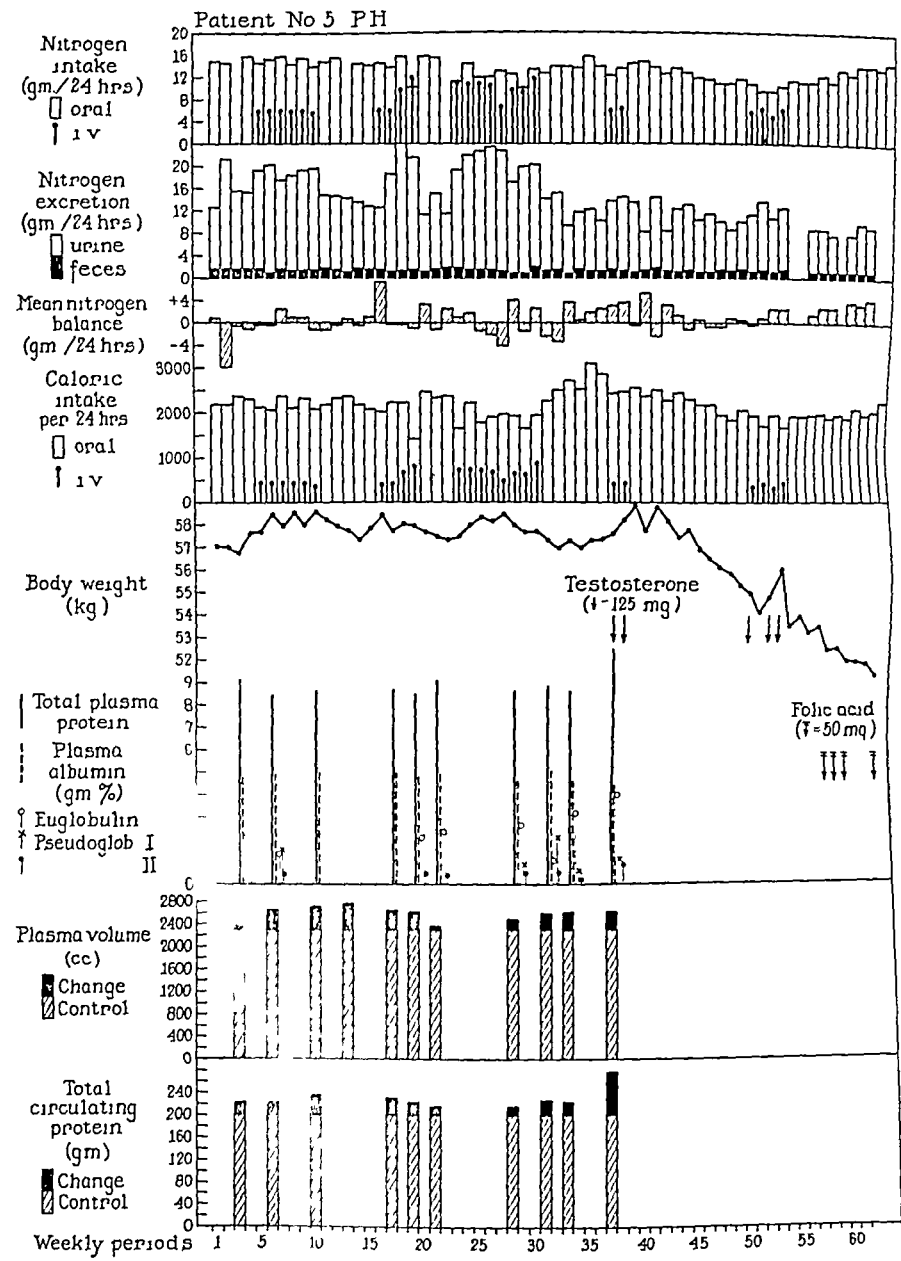


CHART 3

this period The nitrogen equilibrium of this period was maintained for the following six weeks on diet alone

For the next two weeks Amigen and testosterone produced a positive nitrogen balance of 3.34 gms per day which reached equilibrium during the following week when all therapy was discontinued Nitrogen retention of 5.15 gms per day developed in the next week when testosterone without Amigen was resumed This receded again promptly upon the cessation of therapy The patient was in nitrogen equilibrium during this control period of nine weeks as well as in the following two week period of Amigen therapy When testosterone and Amigen were again given for another four week period, the nitrogen balance again became positive at plus 2.32 gms per day In the following control period of two weeks, nitrogen retention of plus 1.87 gms per day was maintained but increased to 3.1 gms per day during the next three weeks when folic acid was given intramuscularly A carry-over effect was noted during the next two weeks when the nitrogen balance remained at plus 3.61 gms per day on diet alone

In this patient with active progressive tuberculosis Amigen produced a retention of nitrogen only early in the experiment when the nitrogen balance was positive or near equilibrium Testosterone and folic acid both produced a marked positive nitrogen balance when given alone or with Amigen

During the early months of the experiment, the patient was partially ambulant However, during the latter part he became progressively worse and remained in bed during the period when Amigen was employed Episodes of fever, chills, and vomiting occurred during and following Amigen infusion

In this patient (No 5) in an earlier period, before the disease became progressive, the use of Amigen was accompanied by a moderate increase of weight up to 2 kgs which fell to the initial level during the control periods Later when his disease became progressive, he lost steadily in body weight irrespective of Amigen with or without testosterone and folic acid The total caloric intake during the early experimental period remained at a constant level of about 2,500 calories During the Amigen administration, the oral caloric intake decreased but the total was maintained by intravenous alimentation In the latter part of the study, the total caloric intake decreased irrespective of treatment with Amigen, testosterone or folic acid The plasma volume showed an increase of 10 per cent following the first period of Amigen administration and decreased slightly during the second control period This again rose following the next period of Amigen

Patient No 6 (P P) M H No 42482 A 32 year old white male first noted weight loss and fatigue in January 1940 His sputum was found to be

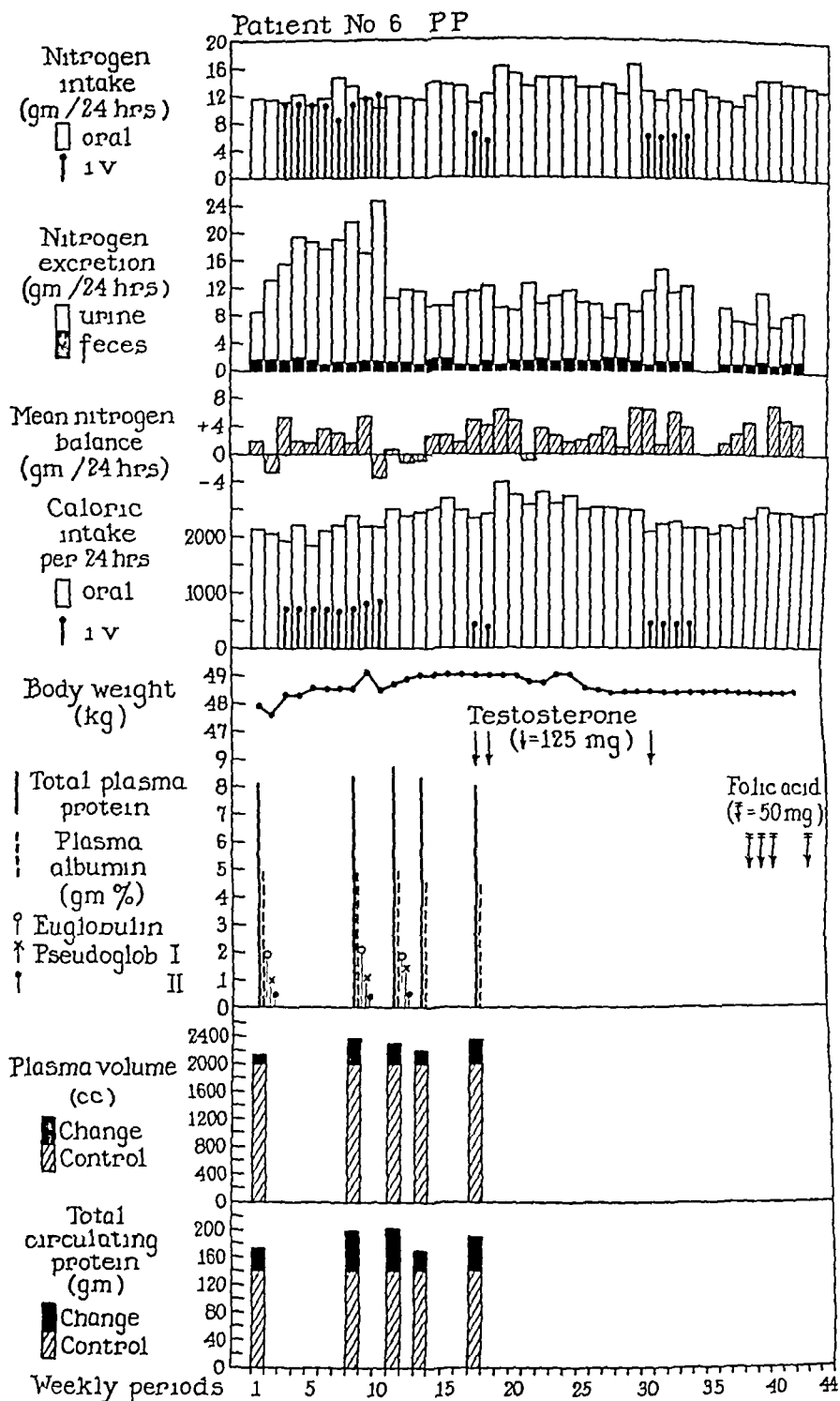


CHART 4

positive for tubercle bacilli at another hospital and the disease was progressive in the right lung, with a large cavity in the mid-lung field. Treatment with artificial pneumothorax supplemented by phrenic crush failed to control the progress. In June 1945, he was admitted to Montefiore Hospital because of profuse hemoptysis. The radiographic examination revealed infiltrations in the apical portions of the left lung with cavity formation. The right lung had fibrotic infiltrations scattered throughout with a large cavity in the upper lobe. Three ounces of sputum were expectorated daily. Bedrest and a high protein diet which was supplemented by intravenous Amigen were employed for therapy. His disease progressed gradually and he died on May 26, 1947.

This patient (No 6, Chart 4) was observed for a two week control period during which he was found to be in nitrogen equilibrium. This was followed by an eight week period of Amigen treatment at which time a positive nitrogen balance of 261 gms per day was obtained. Following the control period of six weeks, he returned to nitrogen equilibrium.

When Amigen plus testosterone were given during the next two week period, a positive nitrogen balance of 441 gms per day was obtained although only half the previous dose of Amigen was injected. A marked carry-over effect was noticed the next week when neither Amigen nor testosterone was given, and this was maintained for the following week on testosterone alone. However, during the succeeding four week control period the nitrogen balance returned as before toward the control level.

After an intermission, the patient was observed for another five week control period, during which a positive nitrogen balance of 312 gms per day was obtained. The increase in nitrogen retention may be explained by the fact that immediately preceding this control period, the patient developed a rectal fistula which confined him to bed. When the fistula began to drain, he was allowed to be ambulant again. The resumption of ambulation²⁵ and clearing of infection^{26, 27} may have contributed to the increase in nitrogen storage. However, administration of testosterone plus Amigen resulted in an elevation of nitrogen balance to plus 491 gms per day. The nitrogen balance dropped to plus 214 gms per day when Amigen and testosterone were discontinued, and again rose to an even higher level of plus 578 gms per day during the next three week period of folic acid administration. A carry-over effect was again observed during the next two weeks on diet alone, the nitrogen balance averaging plus 445 gms per day.

It would seem from these data on this patient that Amigen administration increased the nitrogen retention when the nitrogen balance was close to equilibrium but had no noticeable effect when the nitrogen balance was originally positive. However, both

testosterone and folic acid caused further nitrogen retention even when the nitrogen balance was already strongly positive

Total circulating protein increased from 170 to 200 gms following the eight week period when 2,000 cc of Amigen were given daily, and then fell again to 169 gms during control periods. This rise was due largely to an increase in the plasma volume of more than 20 per cent. Throughout this period there was an increase of body weight of 1.6 kgs.

Discussion

Nitrogen equilibrium is said to exist when the nitrogen intake is equal to the nitrogen excretion. If depletion of tissue protein occurs more rapidly than its replacement, a negative nitrogen balance results. Individuals in the depleted state will retain about 30 gms of protein to replenish the tissues for every gram of plasma protein formed.²⁸ Subjects in good nutrition, with their protein stores saturated, can be maintained in nitrogen balance by a relatively small daily intake of protein if enough calories are ingested.

From Chart 1 in patient No. 1, it is to be noted that this individual was in good nutritional state and in nitrogen equilibrium at the commencement of the experiment. During subsequent periods of treatment, there was a slight increase in the nitrogen intake due to administration of protein hydrolysate intravenously which produced an increase in nitrogen balance, except in the first period of treatment. During control periods when no intravenous therapy was administered on a constant oral intake of nitrogen, the patient maintained his positive balance.

It has been found that in patients in poor nutritional condition²⁹⁻³³ and showing an initial negative balance, improvement in nitrogen balance is more rapid and pronounced, this observation was confirmed in the present study. It can be seen in Charts 2, 3 and 4 that patients 2, 3, 5 and 6 were in poor nutritional state and in or near negative balance at the commencement of the experiment. During subsequent periods of treatment, it can be noted that the additional nitrogen intake, chiefly derived from intravenous administration of hydrolysates, increased the nitrogen balance considerably in a brief period of time. However, during the control period there was a marked drop to a negative nitrogen balance.

In these same patients, studied during a period of nitrogen balance, the treatment and control periods no longer showed wide fluctuations. This is not surprising and is in accordance with the observation of Peters²⁷ who has emphasized the ability of the poorly nourished individual to conserve protein and attain nitro-

gen equilibrium in conditions under which the better nourished individual fails. He suggests that the synthesis of protein may vary inversely with the state of nutrition. Some earlier observations⁶¹ on nephrotic children also pointed to the relationship between ability to store proteins in partial starvation and the patient's nutritional condition.

The variability of nitrogen retention is known to be related to many factors which influence nitrogen storage, such as, ambulation,²⁵ nutritional status, infection, fever and diarrhea.^{26 27} These factors are thought to lead to increased catabolism of the protein or an abeyance in the protein synthesis.^{34 35}

In patients No 1, 4 and 5 during some periods of Amigen administration, there was a fall of nitrogen retention while during most other periods there was a definite increase of nitrogen retention as compared to the control periods. The fall in nitrogen retention could be explained in two patients, No 4 and No 5, by the fact that they were febrile at the time and showed evidence of active tuberculosis. They also showed occasional reactions to the intravenous injections of hydrolysate by severe chills, fever, anorexia and vomiting. It is well known that under conditions of tissue damage and infection, amino acids are not utilized but deaminized and excreted as urea.²⁷

Patient No 1 who had a positive nitrogen balance and was in good nutritional state before the administration of Amigen, showed a decrease in nitrogen storage during the first period of treatment with Amigen. This paradoxical effect can probably be explained by the influence of bedrest and ambulation on nitrogen balance. The increased output of nitrogen due to the immobilization of this patient during the first phase of this experiment might have obscured the effect of Amigen on nitrogen storage. Later in the experiment when the patient remained ambulant during Amigen administration, the expected effect on nitrogen storage was observed.

Normally, the ratio of nitrogen excretion in the stool and urine is about 1:10. The ratio is shifted in favor of increased nitrogen excretion in the urine during Amigen administration. In patient No 3 with frequent diarrhea, the ratio of nitrogen excretion in the stools and urine was about 1:1. In this instance, administration of Amigen tended to reverse the nitrogen excretion in the urine towards the normal ratio. These findings are in accord with results of other authors.⁹

Computed as average values for periods of one or several weeks, the increase of nitrogen output was, as a rule, somewhat smaller than the increase of nitrogen intake during periods of Amigen administration. This resulted in a more positive nitrogen balance.

which varied with each patient and also in the same patient during different phases of the experiment. From Chart 1 it can be noted that Amigen administration in patient No 1, who was in good nutritional state and in positive balance at the commencement of the experiment, resulted in nitrogen retention of 0.2 gms to 5.3 gms per 24 hours during the six week period. In patient No 6 who was in poor nutritional state and in negative balance at the commencement of the experiment, the nitrogen retention during Amigen administration varied from 2.6 to 3.8 gms per 24 hours during the period.

Testosterone propionate in daily doses of 25 mg caused marked nitrogen retention. In patients No 1, 4, 5 and 6, who received this androgen, the increase of nitrogen retention was between 3 and 5 gms per 24 hours. These findings are in accordance with the well established effect of testosterone propionate.^{36, 38} It has been observed by different workers that when patients are given a constant nitrogen intake, the administration of testosterone propionate caused a decrease in the urinary nitrogen with no appreciable change in the fecal nitrogen, so that increased amounts of nitrogen are retained. These changes are apparent by the 2nd or 3rd day and reach their maximum between the 5th and 15th day. In our patients, the nitrogen retention was still seen for some time after testosterone had been discontinued. Furthermore, nitrogen retention caused by Amigen was more pronounced when testosterone was added.

The combined use of folic acid³⁹ and Amigen caused a definite but temporary increase of nitrogen balance in the three patients who received this form of treatment. This experiment confirms the nutritive value of folic acid as pointed out in the literature.

From these experimental data it appears that the use of protein hydrolysates with or without the addition of testosterone or folic acid corrected the nitrogen imbalance in patients with chronic wasting disease.

Several investigators^{40, 41} have studied the utilization of parenterally administered amino acids under varying conditions of total caloric and carbohydrate intake. Schwimmer⁴² concludes that nitrogen balance is not maintained when dietary protein or hydrolysate is not supplemented with adequate caloric intake. Some evidence in man suggests that the injection of amino acids without glucose results in a greater excretion of nitrogen in the urine than when glucose is added. The data indicate that when the daily caloric intake is only 800 calories, nitrogen balance is not achieved, but on an intake of 1,200 calories this can be obtained.^{40, 41} The importance of a high caloric intake in maintaining positive

nitrogen balance in convalescence has been confirmed by recent reports^{26 27}

In all of our patients, the diet was high in carbohydrate and glucose was present in the solution of the protein hydrolysate given parenterally. The caloric intake in these patients was never less than 2,000 and ranged as high as 3,500 calories. Food intake was generally decreased, especially when daily doses of Amigen were given intravenously or in case of febrile reactions caused by disease. In patient No 1, who had quiescent pulmonary tuberculosis with negative sputum and was afebrile, Amigen administration in 2,000 cc doses did not decrease the food intake. However, in patient No 5, with extensive bilateral disease, an active and progressive course with fever and positive sputa, there was a decrease in food intake from the daily average of 2,400 calories during the administration of single doses of Amigen to approximately 1,800 calories during the administration of double doses of Amigen. In the patients No 4 and 6, who also had active and progressive tuberculosis, there was a similar decrease in food intake when double doses of Amigen were injected.

The average plasma volume during the periods of Amigen administration was 3,087 cc in patient No 1 in contrast to the control volume of 2,908 cc. In patient No 3 the average plasma volume was 2,393 cc during Amigen administration and 2,316 cc during oral nitrogen intake. In patient No 4, the plasma volume during Amigen administration was 2,602 cc, during oral intake 2,301 cc. Patients No 5 and 6 showed only slight differences in the plasma volume figures in favor of the intravenous nitrogen route. We are aware of the rather wide range of experimental error in plasma volume determinations, but since we have observed consistent changes, we deem them to be worthy of note.

Concomitantly with the increase in total plasma volume, there was an increase in total circulating protein due largely to the former because the serum protein concentration did not show any rise. There were no consistent changes in the individual protein fractions. The lack of marked serum protein changes is in accordance with the established fact²⁸ that over 96 per cent of the nitrogen retained is utilized for the replenishment of the tissue protein.

Cannon⁴³ has recently pointed out the relationship between protein reserves and antibody production. We began our study originally in an attempt to determine whether prolonged administration of amino acids would have any influence in altering the course of chronic infectious disease. While we realize fully that the interpretation of possible clinical changes is exceedingly difficult in a study of this sort, we have come to the conclusion that

the administration of protein hydrolysate intravenously did not alter the course of the underlying pathological state even though it did correct the nitrogen balance

SUMMARY

1) Nitrogen balance studies were made on six patients with chronic wasting disease. Five of them had chronic pulmonary tuberculosis, three were in positive and two in negative nitrogen balance at the start of the experimental period. The sixth patient had non-specific ulcerative colitis and was also in negative nitrogen balance. Periods of therapy with Amigen, testosterone and folic acid alone or in combination, were alternated with control periods for comparison as to the effect on the course of the disease when patients were in negative and positive nitrogen balance.

2) When patients were at bedrest, Amigen administration did not increase the nitrogen as markedly as when they were ambulant, Amigen improved the nitrogen balance.

3) During periods of activity of the disease, the use of Amigen did not as a rule increase the nitrogen balance. The degree of nitrogen retention during Amigen administration varied inversely with the degree of nitrogen and nutritional deficiency at the time.

4) Folic acid or testosterone increased nitrogen retention more than Amigen alone.

5) Increase in plasma volume and total circulating proteins was frequently seen following proportional to the increase in nitrogen retention.

6) The disease state was not altered by the intravenous administration of protein hydrolysate although the nitrogen imbalance was corrected by the parenteral administration of Amigen.

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RESUMEN

1) En seis enfermos con enfermedades crónicas debilitantes se hizo el estudio del equilibrio nitrogenado. De ellos, 5 tenían tuberculosis pulmonar crónica, tres estaban en equilibrio positivo nitrogenado y dos negativos al principio del periodo experimental. El sexto enfermo tenía una colitis ulcerosa no específica y su equilibrio nitrogenado estaba también negativo. Se alternaron periodos de uso del Amigen, testosterona, y ácido fólico solos o en combina-

ción con periodos de control para comparar el efecto de los equilibrios positivo y negativo nitrogenados sobre la evolución de la enfermedad

2) Cuando los enfermos permanecieron en cama la administración de Amigén no aumentó la retención de nitrógeno, pero cuando deambulaban el Amigen mejoró el equilibrio nitrogenado

3) Durante periodos de actividad de la enfermedad el uso de Amigén no aumentó el equilibrio nitrogenado. El grado de retención de nitrógeno mientras se usó el Amigén varió de modo inverso con el grado de deficiencia nutritiva y nitrogenada en ese tiempo

4) El ácido fólico o la testosterona aumentaron la retención de nitrógeno mas que el Amigén solo

5) El aumento de volumen del plasma total y las proteínas circulantes totales, fué proporcional al aumento de la retención de nitrógeno

6) El estado de la enfermedad no fué alterado por la administración de hidrolizado de proteínas, aunque el desequilibrio nitrogenado fué corregido por la administración parenteral del Amigén

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Report of the Committee on Chemotherapy and Antibiotics

The Use of PAS in Tuberculosis

In an endeavor to accumulate information as to the effectiveness of para-aminosalicylic acid in the various forms of tuberculosis, a total of 150 questionnaires was sent to the larger sanatoria in the United States by the Committee on Chemotherapy and Antibiotics of the American College of Chest Physicians during March 1949. A total of 110 replies was returned.

Only 25 institutions had used PAS or were willing to offer an opinion concerning its use. The total number of patients treated with this drug in this survey was 341. The preponderance of opinion indicated that 12 grams or more of PAS is the desirable daily dosage if it is tolerated in this amount, and that the duration of treatment should be between two and four months. The range of reported dosage generally was from about 5 grams to over 12 grams daily, and the desired duration of treatment was reported from less than two months to six months.

Of the 25 sanatoria reporting experience to some degree with PAS, 13 think that it is helpful in tuberculosis. Only two offered the opinion that it is definitely not helpful in tuberculosis, while 11 had formed no opinion as yet. The various types of tuberculosis in which PAS has been used and the totals of favorable impressions as to its use in those types are as follows: pulmonary 12, tracheobronchial 5, laryngitis 2, draining sinus 1, pleural effusion 2, empyema 1, genito-urinary 3, bones and joints 1, enteritis 1, and milary 1.

Nineteen physicians among those answering the questionnaire had used PAS in combination with streptomycin. Six of these were of the opinion that it has a synergistic or additive effect, while 13 had come to no conclusion as yet.

To summarize briefly, it seems to be the feeling among the men with some experience with the drug that the optimum dose of PAS is 12 grams or more if it is tolerated in this amount, and that the duration of treatment should be from two to four months. PAS seems to have some usefulness in the chemotherapy of various types of tuberculosis, and appears to have some synergistic or additive effect when used in conjunction with streptomycin.

The Use of Streptomycin During Pregnancy

During the years that streptomycin has been used clinically in the treatment of tuberculosis, there has been a feeling of great

hesitancy on the part of many physicians to use this drug in pregnant women, due to the fear of possible severe ill-effects on the hearing and vestibular apparatus of the foetus. In view of this fact, it seemed very desirable to the committee to attempt to establish how well founded this fear may be and to determine the present attitude of chest physicians toward the use of streptomycin during pregnancy. So a questionnaire regarding the use of streptomycin in pregnant women was also sent to 150 institutions where tuberculosis is treated.

From the answers received the committee learned that 29 of the physicians questioned had used streptomycin in a total of 51 such patients. Of the physicians reporting, 11 preferred a daily dosage of 0.5 grams, 16 preferred 1.0 gram, and 2 thought that 2.0 grams daily to be the optimum dose. A majority felt that the optimum duration of treatment in such cases to be from 30 to 60 days. Four physicians preferred to treat the patients entirely as in non-pregnant cases. At the time the reports were received 46 babies had been delivered and no ill effects had been observed in any of them to date. Five had not yet been delivered at that time.

In summary, streptomycin when used during pregnancy seems to have no serious deleterious side-effects on the foetus. The preferred daily dosage among the physicians answering the questionnaire ranges from 0.5 to 1.0 gram, and the duration from 30 to 60 days.

In view of the above favorable reports, it would appear that streptomycin may be used in pregnant women with reasonable safety to the foetus, in doses of 0.5 to 1.0 gram daily, for periods of 30 to 60 days. Since it is of great importance that the present favorable impression be either confirmed or disproved, the Committee on Chemotherapy and Antibiotics would greatly appreciate receiving reports from other physicians who have had experience with streptomycin in such cases.

Urgoiti of La Coruna, Spain, has reported that one of the thiosemicarbazones, designated as TB-1, has shown promising results in experimental tuberculosis. The antituberculosis action of the thiosemicarbazone was first announced by Domagk, Benisch, Mietzsch and Schmidt in 1946 (*Naturw.*, 1946, 10 315). In 1947 the first clinical trials were reported by Moncorps and Kalkhoff (*Med. Klin.*, 1947, 42 812). In 1948 Arold in Weisbaden discussed clinical investigations in which the drug was found useful in tuberculous ulcers, intestinal tuberculosis, and in exudative lesions but not in tuberculous meningitis. He reported that the drug may be injurious to the kidneys, liver, and hematopoietic system.

Investigation of the thiocarbazones has started in the United States. A preliminary report of the action of one of these com-

pounds in experimental tuberculosis in mice was recently reported by Donovan and Bernstein (Am Rev Tuberc , 60 539, October 1949)

Tuberculosis physicians in the United States will await with interest results of further laboratory and clinical investigation of these compounds

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E d i t o r i a l s

THE NEED FOR MORE INTELLIGENT USE OF STREPTOMYCIN IN MANAGEMENT OF PULMONARY TUBERCULOSIS

In January 1944, Schatz, Bugie and Waksman reported their discovery of streptomycin. Less than a year later, in the autumn of 1944, enough laboratory work and animal experiments had been done to justify the cautious use of the drug in humans suffering from miliary, meningeal or far advanced pulmonary tuberculosis. Shortly thereafter patients with a less hopeless prognosis were treated. Soon it became evident that streptomycin was a useful drug in the treatment of tuberculosis. Like other valuable drugs, streptomycin has its limitations as well as its assets and early clinical investigators of the drug were quick to point out that streptomycin was *not* a "cure all" for tuberculosis and that it was *not* a substitute for other proved procedures, such as bed rest and collapse therapy. It was early emphasized in regard to pulmonary tuberculosis that the best end-results would be obtained using streptomycin as an adjunct to other therapeutic measures.

It is now five years since streptomycin was first used in clinical tuberculosis. During this period a wealth of valuable information has been added to our knowledge of the drug to guide physicians in its intelligent use. In spite of the vast amount of knowledge accumulated and the numerous splendid papers written, there is still abundant evidence to indicate that use of streptomycin is too often abused. In many instances the life of the patient may be

jeopardized by injudicious use of the drug in the over-all management of the case

The occurrence of streptomycin-resistant tubercle bacilli is undoubtedly the chief stumbling block in the use of the drug and this factor must constantly be borne in mind by the physician treating tuberculosis. Since present evidence clearly indicates that streptomycin-resistant organisms occur in a majority of patients who have received streptomycin for a period of two to three months or longer it is imperative that the optimum time for the use of the drug be carefully determined in each case. Procedures such as pneumothorax and thoracoplasty and particularly pulmonary resection are most often effective when timed properly in relation to the administration of the drug. The advent of dihydrostreptomycin which lessens the occurrence and severity of toxic side effects, has not changed the picture as regards the phenomenon of drug-resistance.

During the past year several investigators have reported that the appearance of streptomycin-resistant organisms can be considerably delayed in a majority of the patients under study by the administration of para-aminosalicylic acid (PAS) in combination with streptomycin. These preliminary reports are encouraging and if they are sustained by further investigation, it may be hoped that our treatment of certain cases can be modified and improved by such combined therapy. The work of Tempel and Dye regarding intermittent dosage schedules of streptomycin as reported in this issue of "Diseases of the Chest" is also encouraging.

In view of the fact that within a short period of five years streptomycin has become universally accepted as an invaluable aid in the treatment of the various forms of tuberculosis, it seems appropriate at this time to comment on the tremendous achievement of those who have had a share in developing the present knowledge of this drug. Surely this accomplishment is a monument to all the groups, organizations and drug firms, who have worked together in such close and active cooperation, pooling their experience, resources and results to accumulate so much information in such a short time. This experience in the clinical evaluation of streptomycin should serve as a splendid example of what can be accomplished by cooperative effort. Surely this same fine spirit of cooperation, if continued will insure a rapid and thorough clinical evaluation of any new and promising anti-tuberculosis agents which may be discovered in the future.

KARL H PFUETZE MD FCCP Chairman
Committee on Chemotherapy and Antibiotics

THE NEED FOR FURTHER INVESTIGATION AND RESEARCH IN CHEMOTHERAPY AND ANTIBIOTICS

Perhaps it is not an exaggeration to say that in no other field of medicine has the development of antibiotics had so far reaching an effect as in diseases of the chest. It is not only that methods of therapy and approach to the various pathological conditions have been radically changed, for that can be said of almost every other field of medicine. The emphasis lies in the fact that conditions considered previously as untreatable are now being attacked directly, and that as this occurs, a number of conditions, hitherto unknown or unrecognized, are assuming a position of major importance. In this latter category may be placed that group of pneumonic conditions variously classified as atypical pneumonias or virus infections, while in the former are miliary tuberculosis and chronic bronchiectasis of wide distribution.

Through the early sulfa and penicillin days, pneumococcus pneumonia was the chief area of usefulness for these therapeutic agents. It was not long before clinical investigation, following the work of Castex, indicated that penicillin at least, could be used to attack many chronic and acute infections of the bronchi directly by the aerosol method. This not only opened up a new method of approach in treatment, but through the work of Barach, Olsen, Segal and others showed that conditions such as sinus infection and bronchiectasis might yield to this medical treatment.

During all this period, one of the major problems—that of tuberculosis—was in nowise affected. The discovery of another antibiotic, streptomycin, brought the striking and now well-established change in the treatment of this disease. Other new agents have continued to be discovered, they have taken their place in the handling of various conditions, or have been found ineffective for a variety of reasons.

Thus, we find PAS becoming an established medication in tuberculosis, while aureomycin and chloromycetin are promising to be major factors in the control of virus and certain bacterial infections. What is perhaps more surprising, is our very lack of astonishment at the announcement that a new antibiotic has been developed. We have come to expect these almost as regularly as changes in the weather.

These medications, which in one sense have made it so much easier for the chest specialist to treat disease, have, on the other hand, presented him with additional problems that cannot be evaded. When pneumonia or tuberculosis was being treated symptomatically by rest and by minor medicaments, it did not matter too much whether the attending physician had a clear or a hazy

concept of the type of pathology responsible for the disease. The result was not varied in the majority of cases by his knowledge or the lack of it. Today, when he is using antibiotic agents which may attack the disease directly, he must know not only the causative organisms and what their sensitivities may be, but the very nature of the pathological process. This latter information may determine the mode of administration and the necessary adjuncts to accomplish a cure. For example, in acute bronchial infection, an antibiotic may be effective which reaches the disease through the bloodstream. In long standing chronic infection of the bronchi, such an approach may be valueless because of the barriers established between the infection and the blood supply, and the more direct approach of aerosol may be indicated. The limitations of streptomycin in cavitary tuberculosis is another such example. Here the knowledge of this pathology with the inability of streptomycin to penetrate the cavity wall may indicate collapse or surgery as the major portion of the treatment, and the physician is not lulled into a sense of false security by improvement in the early months of treatment.

There is another aspect to this same subject, no less important but perhaps less obvious. This is the necessity of understanding the physiological changes which are occurring and the need for correcting these in addition to the elimination of the infection. This circumstance may be found in a virus pneumonia where the elimination of the infection may find bronchi and bronchioli edematous and filled with secretion, while interalveolar changes handicap both gas exchange and pulmonary circulation. The necessity of correcting these difficulties and of supporting respiration and circulation until a normal status has been reached is no less important than the administration of the newest and most expensive of the antibiotics.

In fact, it is fair to say that these short cuts in treatment, the antibiotics whose value cannot be overemphasized, have placed a greater premium on the art and skill of the physician. It was easier when large numbers of patients were dying of diseases which were enigmas to medical science. If there are successful methods of attack for some of these conditions, as indeed there are, it becomes of prime importance to classify, segregate and catalog them in pathological and physiological reactions and their response to treatment, and to be able to do so when confronted by a clinical picture in a dying patient. A pneumonic process, even if it does respond clinically to antibiotics, may mask a tumor and valuable time is lost during the period of acceptance of congratulations and explaining why the complete disappearance of the pulmonary shadow is taking so long. The tuberculin test and the sputum

examination are likely to be overlooked but never before have they been so important. The one or the other may serve as a definite indication of what should or should not be done.

In this connection, the responsibility of the chest specialist is ever increasing now, when many physicians, without the advantage of training in this specialty, are being called upon to use these antibiotics. This is as it should be, since under our system, the family doctor is the man who sees and treats most illness. But the specialist must investigate and study and collect his observations and opinions. And he must impart through formal courses, meetings, and informal discussions all the information which he may possess to whatever medical men may be interested. This is not an elective procedure, it is his duty and his responsibility to ensure that these miraculous medications are used to the greatest benefit of the general public.

It is likewise important that investigation and research along these lines be continued and increased. The field is so great that no man's experience can cover all aspects of the voluminous studies that are necessary to determine how and when these antibiotics shall be used. These constant studies must be correlated and evaluated and the digest passed on so that all may know what has been accomplished and what further investigation is necessary. This is a task which has been allotted to the Committee on Chemotherapy and Antibiotics of the Council on Management and Treatment of Diseases of the Chest. It is an awesome task not to be taken lightly. Too often have preliminary results been contradicted by long term observation. And too frequently has an obvious fact been shown by further research to be a fiction instead. Yet this task must be done and in keeping with the over-all nature of the field of diseases of the chest, must be correlated with the work of the other committees of this Council, those on Surgery, Collapse and Physiologic Treatment. This information collected and digested is issued from time to time as a report by the committee in question. These reports are not intended to represent a statement of authority nor yet to delineate the only accepted methods of treatment by which the therapy of any physician might be measured. They are rather intended to represent a digest of experience and the current opinion on any drug or treatment. Thus they can be used as a source of information. This special issue of "Diseases of the Chest" represents another function of this Committee. Under the leadership of Dr. Karl Pfuetze, the Committee on Chemotherapy and Antibiotics has compiled and arranged this issue containing recent and authoritative information on antibiotics and chemotherapeutic agents. These being original contributions are not published as a

Committee Report but represent the experience and informations of the authors alone

This is another type of Committee activity in addition to the regular digests of opinion. By such activity it is hoped that the lag between investigation and clinical practice may be shortened so that medical advance as represented by such things as antibiotics may improve the treatment of diseases of the chest as rapidly as is consistent with good scientific experience

EDWIN R. LEVINE, M.D., F.C.C.P., Chairman
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THE GLORY OF TWENTIETH CENTURY MEDICINE

The last 25 years of the 19th century was the most productive era in the history of medicine from the standpoint of determining etiology of human and animal diseases. After Hansen announced the discovery of the bacillus of leprosy in 1874, one organism after another was found to be specific for certain diseases, such as gonorrhea, typhoid fever, anthrax, tuberculosis, lobar pneumonia, glanders, diphtheria, tetanus, brucellosis, cerebrospinal meningitis, bubonic plague, etc., etc. The epoch-making discoveries in parasitology and bacteriology was one of the chief glories of medicine of the 19th century.

Aside from the production of antitoxin for diphtheria and tetanus, little was accomplished in the 19th century by way of treating the diseases whose causes had become known. In the early part of the 20th century, much time and effort were expended searching for specific therapy for the bacterial diseases. As the fourth decade of the 20th century opened, no adequate specific therapy had been found for a sizable number of the most destructive diseases that attack the chest. One discouragement after another had caused many workers to almost lose hope.

When Domagk discovered and reported in 1935 that prontosil has an antibacterial action on hemolytic infection in mice and it was soon observed that infections caused by the gonococcus and meningococcus yielded to this drug, there was a revival of interest in chemotherapy for all of the bacterial diseases.

From this beginning, various sulfonamide compounds were found to be so effective in controlling certain bacterial diseases that they were promptly referred to as "miracle drugs." While these preparations were at the height of deserved popularity, antibiotic substances were introduced for disease control. Penicillin was soon designated the "wonder drug." Only five years ago, the isolation of streptomycin was announced and in 1948 aureomycin was introduced.

Penicillin was found especially helpful in controlling infections with Gram-positive organisms. Streptomycin controlled some of the Gram-negative bacteria which were resistant to penicillin. There remained a number of organisms which were unaffected by penicillin and streptomycin which are controlled by aureomycin.

Practically all of the organisms that result in suppurative conditions of the chest, such as pulmonary abscess and empyema, are sensitive to one or more of these antibiotics. In fact, a synergistic relation has been demonstrated to exist between aureomycin and polymyxin or penicillin *in vitro* and between aureomycin and penicillin *in vivo*.

Most of the organisms which have been responsible for the pneumonias, such as pneumococci and streptococci, are now treated successfully by one or more of these preparations. Even cases of primary atypical pneumonia have been reported to respond to aureomycin. Even the bacillus of Friedlander apparently is sensitive to this antibiotic. Diseases such as brucellosis and tularemia which occasionally attack the lungs and pleura respond to one or more of these preparations.

Several of the rickettsial infections which may produce pneumonitis, such as Q fever, Rocky Mountain spotted fever and typhus fever, respond to aureomycin.

Since the chest yielded up most of its secrets to the surgeon, infections constituted an important hazard in chest surgery. The use of antibiotics has largely removed the dangers of such infections.

Hope was revived in chemotherapy for tuberculosis when a sulfone preparation known as promin was found to suppress experimental tuberculosis in 1940, and again when the bacteriostatic effect of para-aminosalicylic acid (PAS) was discovered in 1943.

Streptomycin was the first antibiotic to yield impressive results on tuberculosis in both animals and humans, with the first report on experimental tuberculosis in December, 1944 and the first on clinical tuberculosis in September, 1945.

Dihydrostreptomycin was announced in 1946. During the present year neomycin was introduced, but has not been released for clinical use except for carefully conducted studies. Although the sulfones, PAS and the antibiotics, including streptomycin and dihydrostreptomycin, have not proved to be bactericidal, they do possess bacteriostatic properties which are proving of value in the treatment of tuberculosis. However, they must be considered only as adjuncts to the usual therapeutic procedures. To date, streptomycin has proved to be the most promising drug in the treatment of tuberculosis. However, it possesses serious limitations such as the resistance which tubercle bacilli develop to it and its

toxic qualities. So far, these have been overcome only in part. Neomycin in the laboratory has proved more active against both pathogenic and saprophytic acid-fast organisms. It is as active against the streptomycin-sensitive as against the streptomycin-resistant tubercle bacilli. Apparently organisms do not develop resistance to it as they do to streptomycin.

Never before has so much interest been manifested by so many physicians or as much money spent in such a short period of time on any treatment of tuberculosis as on the antibiotics during the past five years. A gigantic and well ordered study on the effects of streptomycin, dihydrostreptomycin and PAS has been conducted with the greatest of care by the United States Veterans Administration in cooperation with the Army and the Navy in the treatment of 7,000 tuberculous persons to the benefit of the patients and to the accrual of knowledge. Extensive studies have also been conducted by the Therapy Committee of the American Trudeau Society, the Division of Tuberculosis of the United States Public Health Service, the staffs of hospitals and sanatoriums and private physicians. While a few facts have been established, much remains to be learned.

The papers which appear in this issue of "Diseases of the Chest" clearly state the facts that have been established, indicate work in progress and point to desired goals. Most of the authors were invited to prepare manuscripts for this special issue. All deserve much credit for the expenditure of so much time and effort to make their large store of knowledge available to the readers of this journal throughout the world.

Progress is being made with such rapidity, particularly in the production of new antibiotics that one may momentarily expect better preparations or more efficacious ones to be announced.

It is probable that the chemotherapeutic agents and the antibiotics that have been developed within the past dozen years, and others that may soon be available, will add several years to the span of human life on the earth. Moreover, it is likely that they will contribute to comfort, greater working capacity and efficiency among older people by promptly destroying the diseases in earlier life which result in impairment of function of vital parts when old age is attained. It already appears safe to predict that these epoch-making discoveries in therapy will constitute the chief glory of 20th century medicine.

The Editorial Board of "Diseases of the Chest" is grateful to the Committee on Chemotherapy and Antibiotics and to the Council on Management and Treatment of Diseases of the Chest for this splendid issue of the journal.

J ARTHUR MYERS M.D.

First International Congress on Diseases of the Chest

The First International Congress on Diseases of the Chest will be held at the Forlanini Institute, Rome, Italy, September 17 through 20, 1950. The Congress will be sponsored by the Council on International Affairs of the College in cooperation with the Forlanini Institute. A scientific program covering all phases of diseases of the chest will be presented, as well as an x-ray conference, a motion picture session, and other functions. Professors Attilio Omodei Zorini and Eugenio Morelli, Directors of the Forlanini Institute, will serve as co-chairmen of the committee on arrangements for the Congress. Physicians interested in presenting papers at the Congress are invited to submit titles and abstracts of their material to the program committee for consideration. Please send the information to the Executive Offices of the College, 500 North Dearborn Street, Chicago 10, Illinois.

College Chapter News

CUBAN CHAPTER

A Board of Past Presidents of the Cuban Chapter was organized at the time of a business meeting of the Board of Officers of the chapter held at the Curie Hospital, Havana, on October 31st. The Board is composed of Dr. Gustavo Aldereguia, Chairman, Professor Alfredo Antonetti, Dr. Teodosio Valledor and Dr. Octavio Rivero, Governors of the College for Cuba. Other officers of the chapter attending the meeting were Dr. Antonio Navarrete, Regent of the College for Cuba, Dr. Francisco J. Menendez, President of the Cuban Chapter, Dr. R. Sanchez Acosta, Vice-President and Dr. Carlos Barroso, Secretary.

On November 9 the Cuban Chapter held a meeting at the Academy of Sciences in Havana at which Professor Dante Decanini of Monterrey, Mexico, and Professor Alberto Chattas of Cordoba, Argentina, were guest speakers. The following scientific program was presented:

"Extrapleural Oleothorax,"

Prof. Dante Decanini, Monterrey, Mexico

"BCG Vaccination,"

Prof. Alberto Chattas, Cordoba, Argentina

"Bronchogenic Carcinoma,"

Drs. A. Rodriguez Diaz and V. Anido, Havana, Cuba

"Cysts of the Lung,"

Drs. R. Gomez and Laura Farinas

ILLINOIS CHAPTER

A joint meeting was held by the Illinois Chapter of the College and the Chicago Roentgen Society at the University Club, Chicago, on Thursday, November 10th. Dinner was served at 6:30 p. m. and was followed by a scientific program. The following program was presented:

"Interesting Case Reports,"

C. Giles Cailleteau, M.D. and Marvin Russell, M.D., Hines, Illinois

"The Adult Asymptomatic Chest,"

George M. Landau, M.D., Chicago, Illinois

"Bronchography in Infants,"

Albert H. Andrews Jr., M.D., F.C.C.P., Chicago, Illinois

KENTUCKY CHAPTER

The organizational meeting of the Kentucky Chapter of the College was held at Owensboro, Kentucky, on Thursday, October 6th, at the time of the annual meeting of the Kentucky State Medical Association. Dr Paul A. Turner, Louisville, was elected President of the new chapter, Dr T. Ashby Woodson, Louisville, was elected Vice-President, and Dr Hugh L. Houston, Murray, was elected Secretary-Treasurer. Dr Richard H. Overholt, Brookline, Massachusetts, Past-President and Chairman of the Council on Pan American Affairs of the College, presented a paper at the meeting of the Kentucky State Medical Association and attended the meeting of the new chapter.

The members of the College in Kentucky who were present at the meeting applied for a charter for the Kentucky Chapter which has been submitted to the Board of Regents of the College. The application for a charter was signed by the following College members: Leshe C. Dodson, M.D., Owensboro; John B. Floyd, M.D., Richmond; Rudolph E. Gernert, M.D., Louisville; John S. Harter, M.D., Louisville; Hugh L. Houston, M.D., Murray; Carl C. Howard, M.D., Glasgow; Boyce E. Jones, M.D., Waverly Hills; R. O. Joplin, M.D., Louisville; John B. McHugh, M.D., Outwood; Heinz Oppenheim, M.D., Outwood; Hugo Polderman, M.D., Waverly Hills; J. Frank Stewart, M.D., Waverly Hills; Lawrence A. Taugher, M.D., Louisville; Lawrence O. Toomey, M.D., Bowling Green; Paul H. Turner, M.D., Louisville; T. Ashby Woodson, M.D., Louisville.

MICHIGAN CHAPTER

The Michigan Chapter of the College held a meeting at the Detroit Tuberculosis Sanatorium on November 9th. Dinner was served at 6:30 which was followed by a talk given by Dr. Carl Birkelo, Radiologist at Herman Kiefer Hospital, Detroit, on the subject of "Diagnosis of Diseases of the Chest."

SOUTHERN CHAPTER

At the annual meeting of the Southern Chapter of the College, held in Cincinnati on November 13 and 14, the following officers were elected for the coming year:

David H. Waterman, M.D., Knoxville Tennessee, President
M. Jay Flipse, M.D., Miami, Florida, First Vice-President
Hollis E. Johnson, M.D., Nashville Tennessee, Second Vice-President
George R. Hodel, M.D., Houston Texas, Secretary-Treasurer

WISCONSIN CHAPTER

At the annual meeting of the Wisconsin Chapter held in Milwaukee on October 2, the following officers were elected for the ensuing year:

Carl O. Schaefer, M.D., Racine, President
John P. Fetherston, M.D., Milwaukee, Vice-President
Leon H. Hirsh, M.D., Milwaukee, Secretary-Treasurer

Dr. Leon Hirsh reported that the Milwaukee Metropolitan Section of the Wisconsin Chapter met at the Medford Hotel in Milwaukee on Friday, November 25, 1949. Doctors Timothy R. Murphy and Armin R. Baier spoke on "Pulmonary Function." The presentation was followed by a round table discussion.

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VOLUME XVI

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